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Synthesis of enantiopure carbo- and heterocyclic compounds from the products of benzoate dioxygenase

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Synthesis of enantiopure carbo- and heterocyclic compounds from the products of benzoate dioxygenase

Toby J. Nash

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

April 2019

Declaration of work done in conjunction with others

Computational work reported in chapter 2 on compound **II-29** (page 39) was conducted by Dr. Matthew Grayson (University of Bath).

Compounds **II-66** to **II-70**, reported in chapter 2, were synthesised by Carlos Lopez-Alled (Master's student 2015-16, University of Bath).

All crystal structure data was acquired and processed by Dr. Gabriele Kociok-Kohn (University of Bath).

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Special thanks must also go to my friends and family. In particular, I must thank my partner, Hannah, who has been supporting and patient throughout.

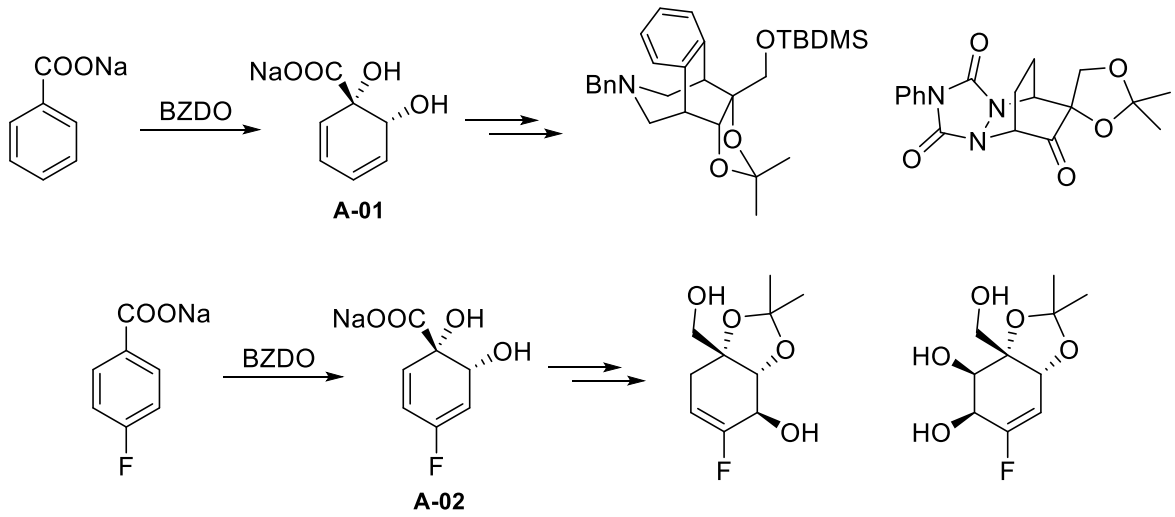
Finally, I would like to thank the Biotechnology and Biological Sciences Research Council (BBSRC) and Almac Group for generously funding this project.

Abstract

Of the threats faced by current and future generations, man-made climate change is perhaps the greatest. In order to combat climate change, chemists must contribute to reducing the environmental impact of synthetic chemistry. Biocatalysis could be a useful tool with which to combat climate change, since environmentally benign syntheses of complex molecules can be achieved through its use.

Benzoate dioxygenase (BZDO) enzymes allow access to arene *ipso,ortho*-diols through the dearomatisation of sodium benzoate (scheme A-01). This enantiopure building block has previously shown utility in the synthesis of natural products and cyclitols.

This thesis sought to expand on the known chemistry of arene *ipso,ortho*-diol **A-01** through the synthesis of arene diol derived heterocycles and asymmetric epoxidation organocatalysts (scheme A-01). In addition to these themes, the microbial oxidation of sodium 4-fluorobenzoate has been achieved, providing fluoro-arene *ipso,ortho*-diol **A-02**. The reactivity of fluoro-arene diol **A-02** has been probed through a number of oxidative transformations.



Scheme A-01: Examples of synthesised molecules reported within.

Table of Contents

Abbreviations

2,2-DMP	2,2-dimethoxypropane
3D	three dimensional
Ac	acetate
AIBN	azobisisobutyronitrile
Bn	benzyl
Bs	benzenesulfonyl
Bz	benzoyl
BPDO	biphenyl dioxygenase
Bu	butyl
BZDO	benzoate dioxygenase
COSY	homonuclear correlation spectroscopy
*m*CPBA	*meta*-chloroperoxybenzoic acid
d	doublet
DAST	(diethylamino)sulphur trifluoride
DCC	*N,N'*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
L–(+)-DET	(+)-diethyl L-tartrate
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N,N*-diisopropylethylamine (Hünig's base)
DMAP	*N,N*-dimethylaminopyridine
DME	dimethoxyethane
DMEDA	*N,N'*-dimethylethylenediamine
DMF	dimethylformamide
DMM	dimethoxymethane
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
DPPF	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
e.e.	enantiomeric excess
Et	ethyl
Equiv.	equivalents

HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
hv	light
IBX	2-iodoxybenzoic acid
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
Me	methyl
MOM	methoxymethyl
MTAD	4-methyl-1,2-4-triazoline-3,5-dione
NBA	*N*-bromoacetamide
NBS	*N*-bromosuccinimide
NDO	naphthalene dioxygenase
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear overhauser effect spectroscopy
OTf	triflate
q	quartet
p	*para*
PAD	potassium azodicarboxylate
PCC	pyridinium chlorochromate
Pd/C	palladium on carbon
Ph	phenyl
Pr	propyl
PTAD	4-phenyl-1,2-4-triazoline-3,5-dione
R_f	retention factor
RT	room temperature
SIBX	stabilised 2-iodoxybenzoic acid
t	*tert*
t	triplet
T3P®	propylphosphonic anhydride solution

TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TDO	toluene dioxygenase
TFA	trifluoroacetic acid
THDMS	*tert*-hexyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPP	tetraphenylporphyrin
Ts	tosyl
*p*TSA	*para*-toluenesulfonic acid
UV	ultraviolet

Introduction to microbial dearomatisation chemistry

The importance of catalysis in synthesis

The diminishing supply of fossil fuels and of catalytically valuable transition metals, and the ever-increasing threat of man-made climate change are two of the greatest challenges faced by current and future generations. Current synthetic methods are highly reliant on the use of transition metals for catalysis and often require reagents which are known to pose significant environmental risks. Over previous decades, synthetic chemists have conducted vital research to help mitigate the risks posed by these environmental issues, however the development of environmentally benign synthetic methodologies remains of vital importance.

In addition to environmental concerns, there is also a continuing demand to synthesise novel organic molecules for a variety of applications. This demand is partly pharmaceutically driven due to, for example, the increasing prevalence of antibiotic resistance[1-3] and the ongoing challenge to find effective treatments for cancer.[4, 5] As such, it is necessary that routes to novel organic compounds are also thoroughly researched.

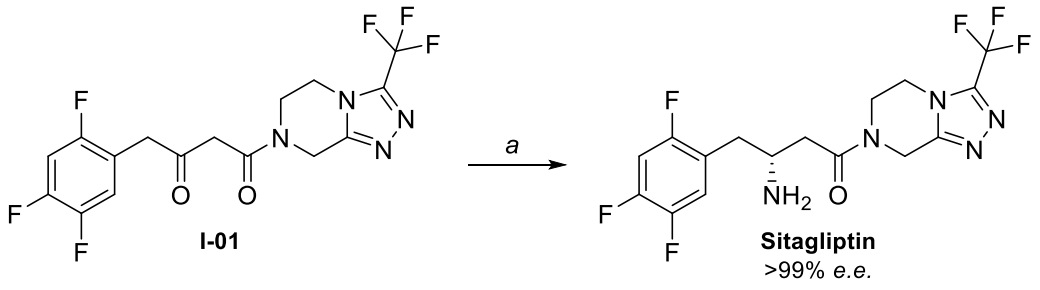
Catalysis – the increase in rate of a reaction by the addition of a reagent that is not itself consumed – allows reactions to be conducted efficiently and economically on multi-tonne scales. The pharmaceutical, polymer and petroleum industries consequently rely heavily on catalysis, which is evident from 90% of industrially produced chemicals requiring at least one catalytic reaction to synthesise.[6] Many catalytic reactions currently in use, however, cannot be considered as being environmentally benign processes, since they fail to fulfil several criteria of green chemistry (figure I-01).[7]

Figure I-01: Principles of green chemistry.[7]

Biocatalysis is the application of enzymes to catalyse chemical reactions and offers many benefits over more traditional catalytic methods.[8, 9] Biocatalysts tend to be non-toxic, environmentally benign and used under ambient reaction conditions. Furthermore, enzymes are also highly regio- and stereo-selective whilst offering extremely high catalytic turnovers, with reactions requiring typical catalyst loadings of between 10^{-6} and 10^{-9} mol%. The low environmental footprint of biocatalysts coupled with their high selectivity make them an attractive candidate for use in industrial scales syntheses.

Biocatalysis can be conducted using either isolated enzymes or whole-cells, with each method offering contrasting advantages and disadvantages.[9] Enzyme extracts are often favoured over whole-cells for use in biocatalysis, since reactions with enzymes involve simple apparatus and tolerate higher substrate concentrations. However, use of isolated enzymes requires the addition of cofactors. Additionally, not all enzymes are isolable since denaturation can occur on removal from their parent cell. In contrast to this, whole-cell biotransformations do not require addition of supplementary cofactors, however specialist equipment is often necessary and substrate concentrations are often reduced when compared to using isolated enzymes. Substrate and product solubility can also be problematic when using whole cells, as biotransformations must be conducted in aqueous media.

One of the successes of biocatalysis in pharmaceutical synthesis is in the manufacture of Sitagliptin.[6, 10] Sitagliptin – the active ingredient in Januvia™ - is used in the management of type 2 diabetes and made sales of $4.1 billion for Merck in the calendar year of 2012. A transaminase was used in the synthesis of Sitagliptin to enantio- and chemo-selectively convert ketone **I-01** to amine containing Sitagliptin in >99% *e.e.* (scheme I-01). The transaminase used was developed through 11 rounds of directed evolution using extensive high-throughput screening, resulting in an enzyme that possessed 4 orders of magnitude greater activity than the original transaminase. Other desirable features were also present in the enzyme, such as its ability to endure substrate concentrations as high as 100 g/L. This biocatalytic reaction was judged to make the overall synthesis of Sitagliptin superior to the previous route, which utilised rhodium-catalysed asymmetric hydrogenation, and earned Merck and Codexis the 'Presidential Green Chemistry Challenge Award' in 2010.



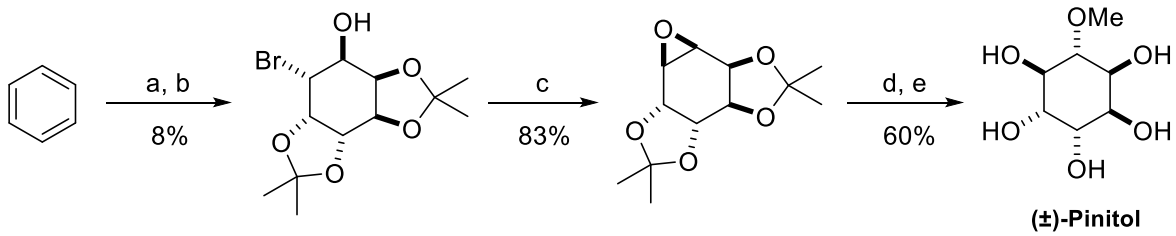
Scheme I-01: Transaminase reaction used in the synthesis of Sitagliptin. *a*) Arthrobacter transaminase, isopropylamine, DMSO, water, pH 8.5.

Chemical dearomatisation strategies

Dearomatisation chemistry allows the synthesis of highly functionalised organic molecules from simple aromatics, which themselves are often inexpensive and abundant. The clear utility of dearomatisation chemistry has led to efforts by several research groups to develop chemical methodologies to achieve this. However, whilst the oxidation of alkenes can be achieved readily using a variety of reagents, the oxidation of aromatic compounds remains challenging on account of their conjugated, aromatic π-system possessing high stability. A comprehensive review on chemical dearomatisation methods has been recently published by Sarlah.[11]

Dearomatisation methods for monocyclic arenes can be broadly categorised into reductive, oxidative, transition metal-mediated and cycloaddition-based methodologies.[11] The Birch reduction, first reported in 1944, effects the sodium mediated dearomatisation of arenes to cyclohexa-1,4-dienes,[12] whilst arenes may also be reductively dearomatized through metal hydrogenation. Metal catalysed procedures for dearomatisation employ stoichiometric quantities of metals in order to form η^2-aryl metal complexes, destabilising the aromatic character of the arene and facilitating its reaction with electrophiles.[13]

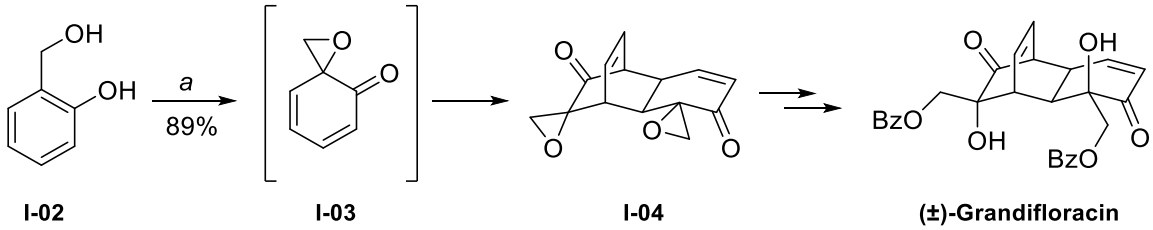
One procedure for oxidative dearomatisation was reported by Motherwell in 1995.[14] Motherwell reported the oxidative dearomatisation of benzene, allowing the synthesis of a range of polyoxygenated cyclohexanes and cyclohexenes. Motherwell found that, upon treating benzene with a stoichiometric quantity of OsO_4 and irradiating the resulting solution with UV light, charge-transfer between the arene and OsO_4 could be induced, ultimately resulting in the dihydroxylation of benzene. In 1997, Motherwell went on to synthesise (±)-Pinitol using this chemistry (scheme I-02), however only a catalytic quantity of OsO_4 was required in this instance.[15] Despite the utility of this chemistry, the use of OsO_4 in this reaction precludes its use for large scale, industrial application.



Scheme I-02: Synthesis of (±)-Pinitol reported by Motherwell.[15] *a*) OsO_4, *hv*, $NaBrO_3$. *b*) *p*TSA, acetone, water. *c*) K_2CO_3, MeOH. *d*) Al_2O_3, MeOH. *e*) HCl, THF, water.

In addition to Motherwell's research, the oxidation of 2-substituted phenols has also been shown to result in dearomatisation of their aromatic π-systems. This chemistry has been used by both Stoltz[16] and Quideau[17] in the synthesis of (**±**)-grandifloracin, a compound that has shown anti-austerity activity against pancreatic cancer cells.[18] Upon treating salicyl alcohol **I-02** with $NaIO_4$, Stoltz and co-workers

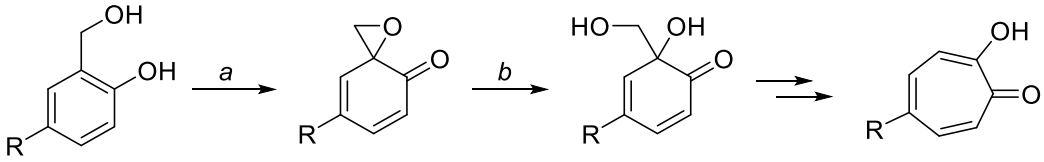
report that epoxide **I-03** forms as a transient species before spontaneously dimerising to form (bis)epoxide **I-04** (scheme I-03). **I-04** may then be converted to (±)-grandifloracin and analogues thereof.



I-02 **I-03** **I-04** **(±)-Grandifloracin**

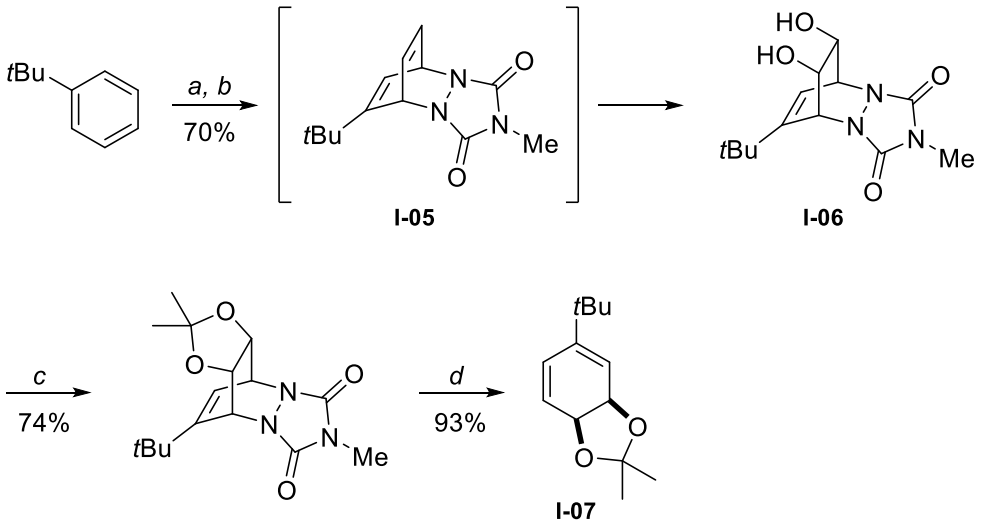
Scheme I-03: Dearomatising oxidation of salicyl alcohol en route to (±)-Grandifloracin.[16] *a*) $NaIO_4$, water.

Bugg *et al.* have further explored the reaction of salicyl alcohols with $NaIO_4$, resulting in the isolation of several epoxides similar in structure to transient epoxide **I-03** (scheme I-03).[19] Whilst dimerization of the 5-substituted epoxides was also reported by Bugg, the rate of dimerization differed depending on the substituted group. Following their isolation and characterisation, epoxides were treated with *Aspergillus niger* epoxide hydrolase to give diols, before being converted to substituted tropolones (scheme I-04).



Scheme I-04: Synthesis of substituted tropolones from salicyl alcohols using a chemical dearomatisation strategy.[19] *a*) $NaIO_4$, water. *b*) *A. niger* epoxide hydrolase.

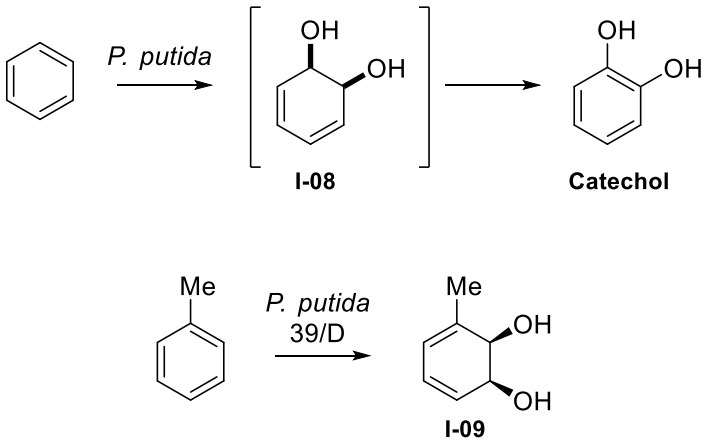
In 2016, Sarlah *et al.* reported the photochemically induced dearomatisation of a range of aromatic compounds.[20] It was discovered that, upon treating arenes such as *t*-butyl benzene with MTAD and exposing the solution to visible light, a [4+2] cycloaddition could be induced (scheme I-05). OsO_4 catalysed dihydroxylation of the resulting diene **I-05** occurred exclusively at the non-substituted alkene to give isolable diol **I-06**. Acetonide protection of the diol and removal of the MTAD group furnished diene **I-07**. Through using this approach, Sarlah synthesised a range of cyclitols and aminocyclitols.



Scheme I-05: Photochemical dearomatisation of *t*-butyl benzene, resulting in diene **I-07**.[20] *a*) MTAD, *hv*, CH_2Cl_2. *b*) OsO_4, NMO, *p*$TsNH_2$, water, acetone. *c*) *p*TSA, 2,2-DMP, CH_2Cl_2. *d*) N_2H_4, $CuCl_2$.

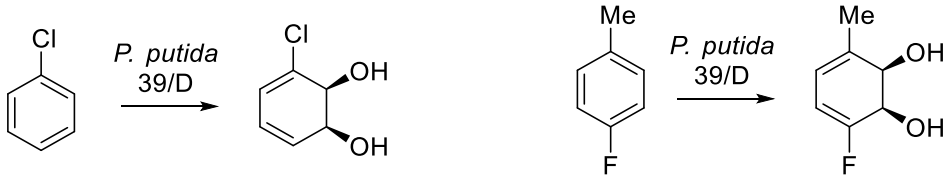
Microbial *ortho,meta*-dihydroxylation of arenes

Due to the many benefits conferred by biocatalytic approaches to synthesis, it is of great interest to utilise biocatalysis for dearomative chemistry. In 1968, Gibson first reported arene diol **I-08** as an intermediate in the conversion of benzene to catechol by a strain of *Pseudomonas putida* (scheme I-06).[21] Later, it was found the a chloro-arene *ortho,meta*-diol accumulated when chlorobenzene was fed to the wild-type strain of *Pseudomonas putida*.[22] Further to this work, Gibson subsequently reported the isolation of arene diol **I-08**, which was found to accumulate in cells of a mutant strain of *P. putida* – *P. putida* 39/D.[23] Gibson and co-workers suggested that the accumulation of arene diol **I-08** was caused by deactivation of the dihydrodiol dehydrogenase of the wild-type organism. In addition to the microbial dearomatisation of benzene, *P. putida* 39/D was also found to dihydroxylate toluene enantioselectively to furnish arene diol **I-09** (scheme I-06).



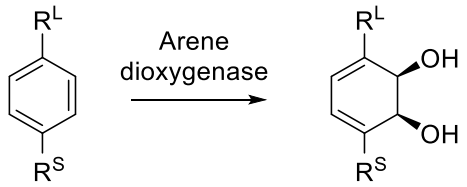
Scheme I-06: Biosynthesis of catechol from benzene (top)[21] and microbial oxidation of toluene to arene diol **II-09** (bottom).[23]

Following Gibson's pioneering research, several other dioxygenase enzymes have been reported to dearomatize aromatics, with each being classified based on the substrate it was first reported to metabolise. Consequentially, the dioxygenase enzyme present in *P. putida* 39/D is classified as toluene dioxygenase (TDO), however this enzyme has also been shown to dearomatize ethylbenzene,[24] chlorobenzene and *para*-halotoluenes (scheme I-07).[25] Other known arene dioxygenases include naphthalene dioxygenase (NDO),[26] biphenyl dioxygenase (BPDO)[27] and benzoate dioxygenase (BZDO).[28]



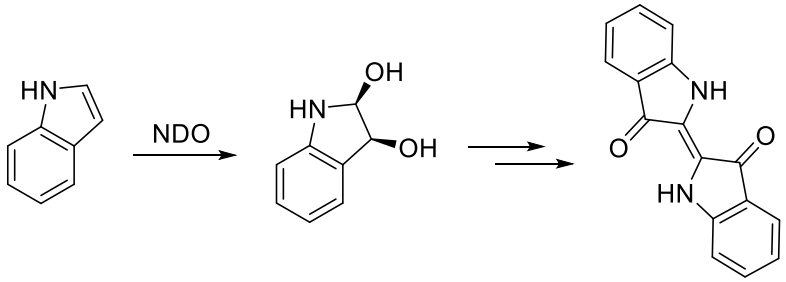
Scheme I-07: Microbial oxidation of chlorobenzene (left) and 4-fluorotoluene (right).[25]

In 1993, Boyd *et al.* developed a widely applicable predictive model for the enantio- and regio-selectivity of microbial arene *ortho,meta*-dihydroxylations (scheme I-08).[29,30] Boyd found that, in the case of 1,4-disubstituted benzenes, dihydroxylation occurs *ortho,meta*- to the more sterically demanding substituent. It was additionally found that, where R^L is significantly more sterically demanding than R^S, the enantioselectivity of the reaction was greater, whereas enantioselectivity decreases on convergence of the steric profile of the substituents.



Scheme I-08: General selectivity observed in the *ortho,meta*-dihydroxylation of aromatics with arene dioxygenases.[29, 30]

Due to the substrate promiscuity of TDO, NDO and BPDO, as well as the commercial availability of arene diols arising from their use, there are numerous examples of arene *ortho,meta*-diols being used in synthesis. Imperial Chemical Industries PLC were the first company to report the use of an arene diol in synthesis, using an arene diol to synthesise polyphenylene in 1983.[31] Gibson later reported the *cis*-dihydroxylation of indole, the product of which was a transient intermediate in the biocatalytic synthesis of indigo (scheme I-09).[32]



Scheme I-09: Synthesis of indigo through the microbial dihydroxylation of indole.[32]

Cyclitol synthesis is of great interest to synthetic chemists, primarily as they are a class of compounds known for possessing a diverse range of biological activity.[33-35] In the 1980s, Ley reported the use of microbial arene oxidation chemistry in the synthesis of several cyclitols from benzene.[36, 37] Synthesised cyclitols included (+)-Pinitol and (+)-Conduritol F (figure I-02). In addition to cyclitols, Hudlický has reported the synthesis of aminocyclitols from benzene,[38] whilst Boyd has demonstrated the synthesis of carbasugars,[39] providing a library of highly functionalized, enantiopure cyclohexanes that can be easily accessed from arenes using biocatalysis.

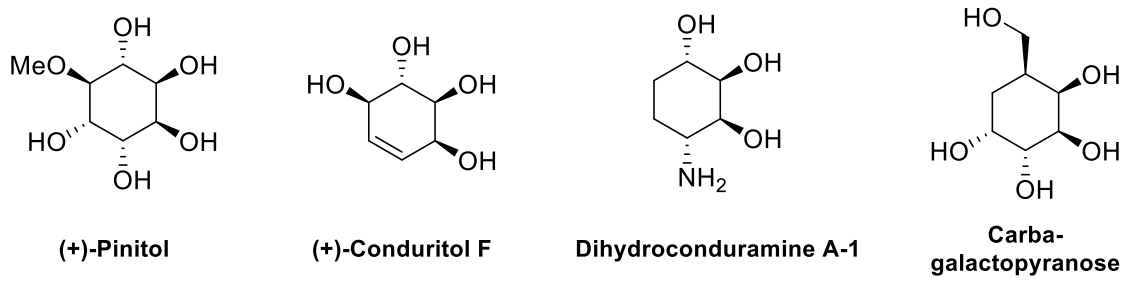
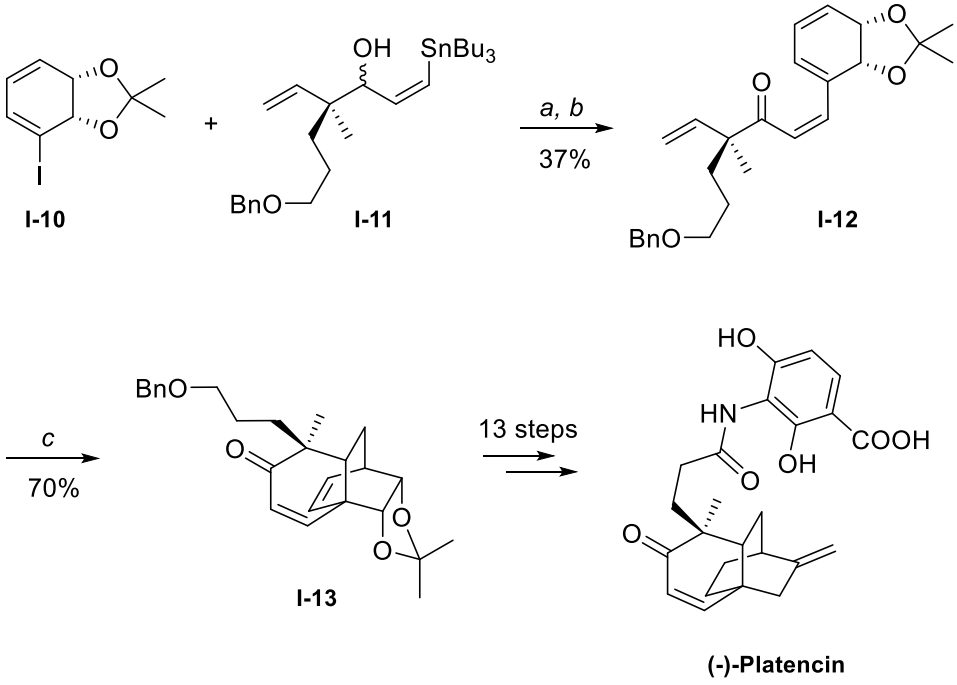


Figure I-02: Cyclitols and aminocyclitols synthesised using microbial arene oxidation.

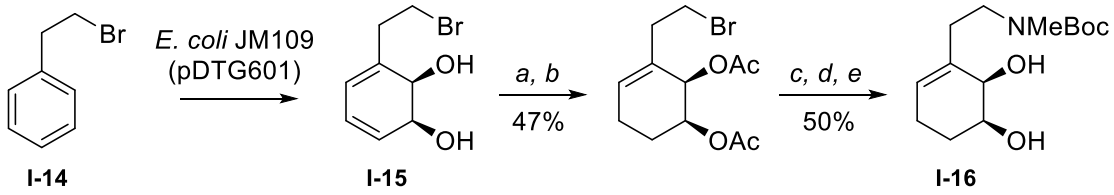
Aside from highly functionalised cyclohexanes, arene *ortho,meta*-diols have also been used extensively in the synthesis of natural products and biologically active compounds. In 2015, Banwell achieved the total synthesis of the terpenoid (–)-Platencin from **I-10**.[40] The core carbocyclic structure of (–)-Platencin is synthesised in the first 3 steps of its synthesis through Stille coupling between dienyl iodide **I-10** and stannane **I-11**, followed by oxidation of the alcohol to give **I-12** and finally an intramolecular cycloaddition to give **I-13**. Overall, Banwell achieved the synthesis of (–)-Platencin in 16 steps from arene diol derived diene **I-10** (scheme I-10). This particular synthesis is of note because (–)-Platencin has been proven to be a potent inhibitor of enzymes involved in bacterial fatty acid biosynthesis and has shown potent *in vitro* activity against a range of bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* (VREF).



Scheme I-10: Banwell's synthesis of (–)-Platencin.[40] *a*) $Pd(Ph_3)_4$, CuI, CsF, DMF. *b*) DMP, pyridine, CH_2Cl_2. *c*) toluene, reflux.

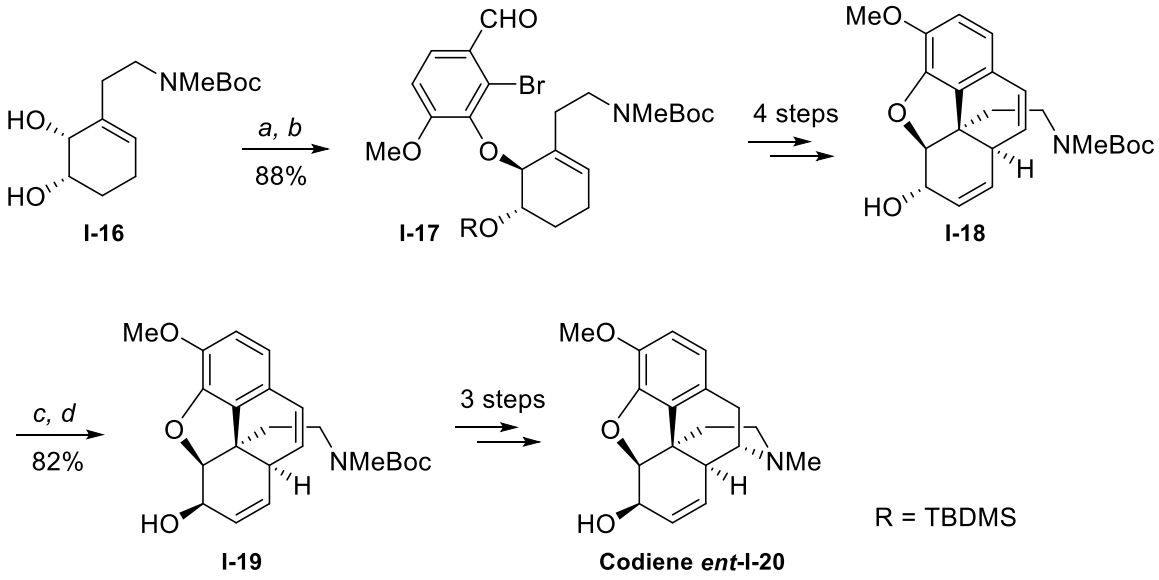
Several alkaloids have also been synthesised using arene *ortho,meta*-diols as starting materials, including (+)-Brunsvigine[41] and (+)-Montabuphine.[42] However, one of the most intriguing total syntheses of an alkaloid is that of Codeine by Hudlický in 2009. Hudlický was able to demonstrate how

both enantiomers of Codeine could be synthesised from a single arene *ortho,meta*-diol.[43] Following the microbial oxidation of arene **I-14** by *E. coli* JM109 (pDTG601) – a recombinant strain of *E. coli* that overexpresses the TDO enzyme – diol **I-16** was synthesised from arene diol **I-15** in 5 steps (scheme I-11). Diol **I-16** was the point of enantio-divergence in the synthesis of both enantiomers of Codeine.



Scheme I-11: Initial steps in Hudlický's synthesis of Codeine.[43] *a*) PAD, AcOH, MeOH, 0°C. *b*) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 0°C. *c*) $MeNH_2$, K_2CO_3, THF, -40°C to RT. *d*) Boc_2O, DMAP, CH_2Cl_2, RT. *e*) MeONa, MeOH, RT.

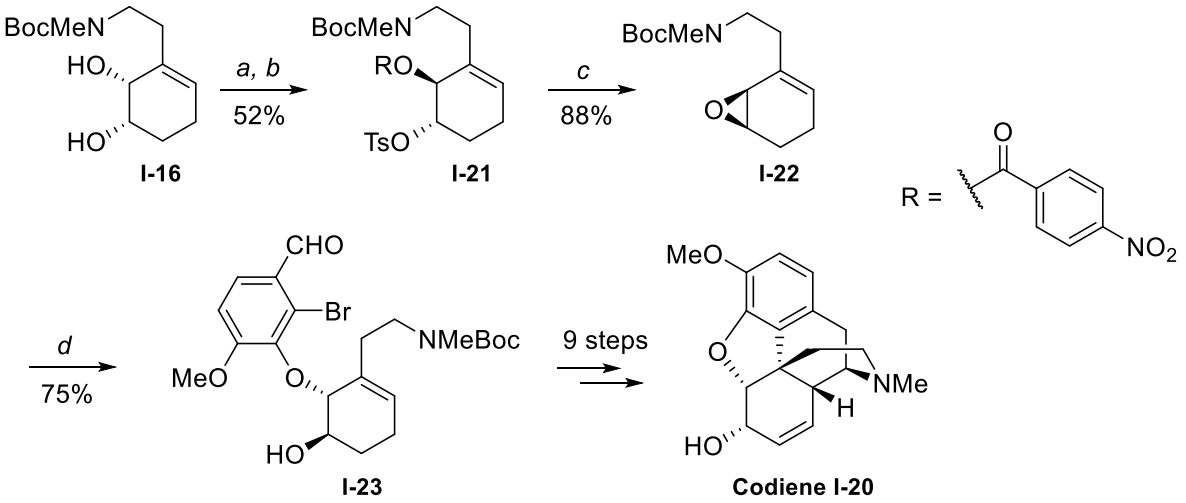
In the synthesis of Codeine *ent*-2, the least hindered alcohol of diol **I-16** is initially protected as a TBDMS ether, followed by Mitsunobu inversion of the remaining non-protected alcohol, using 2-bromo-3-hydroxy-4-methoxybenzaldehyde as a nucleophile, to give **I-17** (scheme I-12).[43] Following the construction of the carbocyclic scaffold of Codeine, the alcohol of **I-18**, previously introduced during the microbial oxidation, is inverted to give alcohol **I-19** (scheme I-12). Further derivatisation of **I-19** gives Codeine ***ent*-I-20**, the non-natural enantiomer.



Scheme I-12: Key steps in the synthesis of Codeine ***ent*-I-20** from diol **I-16**.[43] *a*) TBDMSCl, imidazole, CH_2Cl_2, -78°C to RT. *b*) *n*-Bu_3P, DIAD, 2-bromo-3-hydroxy-4-methoxybenzaldehyde, THF, 0°C to RT. *c*) IBX, DMF, RT. *d*) $NaBH_4$, $CeCl_3.H_2O$, MeOH, 0°C.

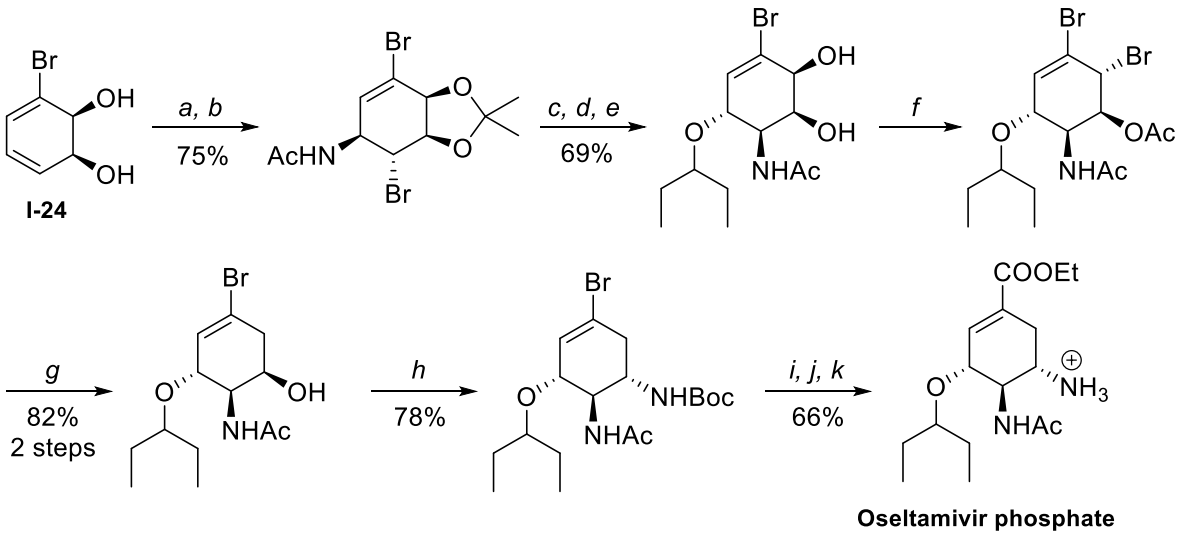
In the synthesis of the natural enantiomer of Codeine, a modified strategy was required to obtain the desired stereochemistry (scheme I-13). Following the Mitsunobu inversion and tosylation of diol **I-16**, an epoxide was formed by reacting **I-21** with sodium methoxide. Epoxide opening of **I-22** with Potassium 2-bromo-3-formyl-6-methoxyphenolate gave **I-23**, which was then subjected to similar conditions to those employed in the synthesis of Codeine ***ent*-I-20** to furnish Codeine **I-20**, the natural enantiomer of Codeine. Hudlický's comprehensive research demonstrates how the stereochemistry

obtained from the microbial oxidation of arenes may be manipulated in order to gain access to valuable compounds.



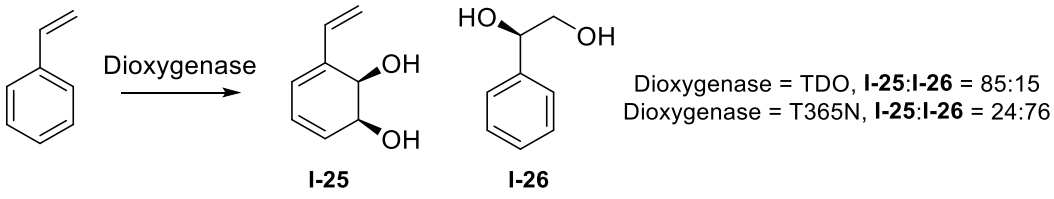
Scheme I-13: Synthesis of Codeine **I-20** as reported by Hudlický.[43] *a*) DIAD, PPh_3, 4-nitrobenzoic acid, THF, 0°C. *b*) TsCl, NEt_3, DMAP, CH_2Cl_2, 0°C to RT. *c*) NaOMe, MeOH, THF, 0°C. *d*) Potassium 2-bromo-3-formyl-6-methoxyphenolate, 18-crown-6, DME, DMF, 80°C.

The anti-influenza agent oseltamivir phosphate (Tamiflu®) generated sales of $3.6 billion in 2009. Due to its clinical success, three separate research groups – led by Fang, Banwell and Hudlický – have made efforts to synthesise oseltamivir phosphate from arene *ortho,meta*-diols.[44-46] The first synthesis of oseltamivir phosphate from an arene diol was reported by Fang in 2008, using bromo-arene diol **I-24** as a (commercially available) starting material. Fang achieved the enantioselective synthesis of oseltamivir phosphate in 11 steps and in a yield of 21% from bromo-arene diol **I-24** (scheme I-14).



Scheme I-14: Fang's synthesis of oseltamivir phosphate.[44] *a*) *p*TSA, 2,2-DMP, acetone, 0°C to RT. *b*) $SnBr_4$, NBA, water, MeCN, 0°C. *c*) LHMDS, THF, -10°C to 0°C. *d*) 3-pentanol, $BF_3.Et_2O$, -10°C to 0°C. *e*) HCl, MeOH, 50°C. *f*) α-acetoxy-isobutyryl bromide, THF, 0°C to RT. *g*) $LiBHEt_3$, THF, 0°C to RT. *h*) DDQ, PPh_3, nBu_4NOCN, MeCN, RT; then *t*BuOH, reflux. *i*) CuI, KI, DMEDA, *n*BuOH, 120°C. *j*) $Pd(OAc)_2$, CO, NaOAc, EtOH, RT. *k*) H_3PO_4, EtOH, 50°C.

Due to the impressive substrate scope of wild-type arene *ortho,meta*-dioxygenase enzymes, there has been little need to conduct engineering on the enzymes to increase their substrate promiscuity. Consequentially, there has only been one reported effort to engineer the TDO enzyme, conducted by Carrera, Rodríguez-Giordane and co-workers in 2017.[47] The authors cited the lack of regio- and stereo-diversity of dioxygenase catalysed oxidations as motivation for researching this area. Three mutant TDO enzymes – I324F, T365N, F366V – were generated and tested in the microbial oxidation of four mono-substituted areas and indene. Whilst in the majority of cases the activity of the mutant enzymes did not differ greatly from the wild-type enzyme, in the oxidation of styrene with mutant T365N a notable difference in regioselectivity was reported (scheme I-15). Due to the proven success of arene *ortho,meta*-diols in synthesis, it is likely that research into engineering the TDO enzyme will continue to be conducted in the future.

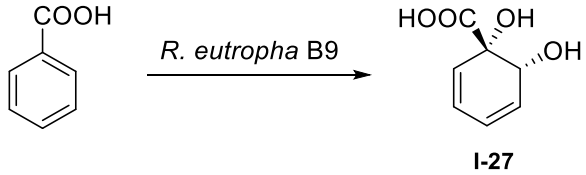


Scheme I-15: Microbial oxidation of styrene using wild-type TDO and TDO mutant T365N.[47]

In addition to the uses of arene *ortho,meta*-diols in the synthesis of natural products, efforts have also been made to synthesise organocatalysts, chiral auxiliaries and ligands from arene *ortho,meta*-diols.[48-50] These efforts have been detailed in the introduction to chapter 3, "Synthesis and testing of a novel epoxidation catalyst".

Microbial *ipso,ortho*-dihydroxylation of benzoic acid

The biosynthesis of catechol through the oxidation of benzoic acid has been a known biosynthetic pathway since 1948.[51] In 1971 Reiner and Hegeman reported the accumulation of an intermediate in this pathway, arene *ipso,ortho*-diol **I-27** (scheme I-16), in a mutant strain of *Ralstonia eutropha* (formerly classified as *Alcaligenes eutrophus*).[52] The oxygenase enzyme present in *Ralstonia eutropha* B9 was therefore termed benzoate dioxygenase (BZDO). In addition to non-substituted benzoic acids, the microbial of oxidation of several substituted benzoic acids has also been reported using *Ralstonia eutropha* B9.[53-55]



I-27

Scheme I-16: Microbial oxidation of benzoic acid using *Ralstonia eutropha* B9.[52]

Through conducting isotopic labelling experiments using $^{18}O_2$, Reiner and Hegeman suggested that the formation of arene diol **I-27** occurs through a peroxide intermediate.[28] In 2015, Lipscomb and co-workers conducted a more detailed mechanistic study into the mode of action of the BZDO enzyme.[56] Lipscomb ascertained the roles of the Rieske iron-sulfur cluster and the mononuclear Fe(II) located in the active site of BZDO through the use of single turnover enzyme experiments and computational chemistry.

In comparison to arene *ortho,meta*-diols, synthetic uses of arene *ipso,ortho*-diols have been less comprehensively studied. A number of factors are likely to have contributed to this, including the limited substrate scope of the BZDO enzyme and the low stability of arene *ipso,ortho*-diols.[52, 53, 55, 56] Nonetheless, the microbial *ipso,ortho*-dihydroxylation of benzoic acid remains highly valuable due to the generation of an enantiopure, tetra-substituted carbon from an inexpensive starting material. Furthermore, the number of synthetic transformations one may perform on arene diol **I-27** is vast (figure I-03). As such, the *ipso,ortho*-dihydroxylation of benzoic acid has still been shown to be of great utility in the synthesis of an array of enantiopure compounds.

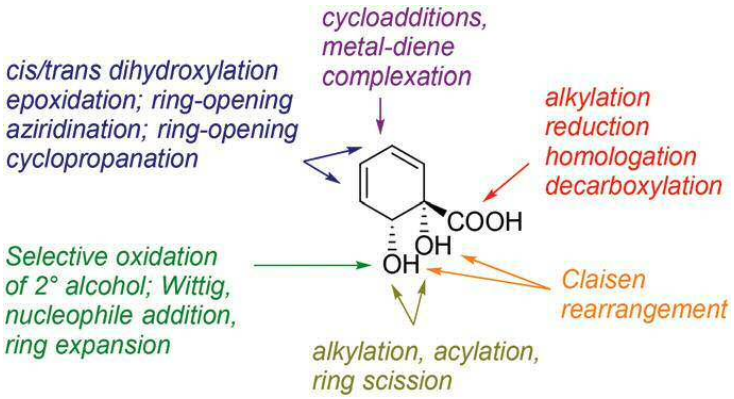
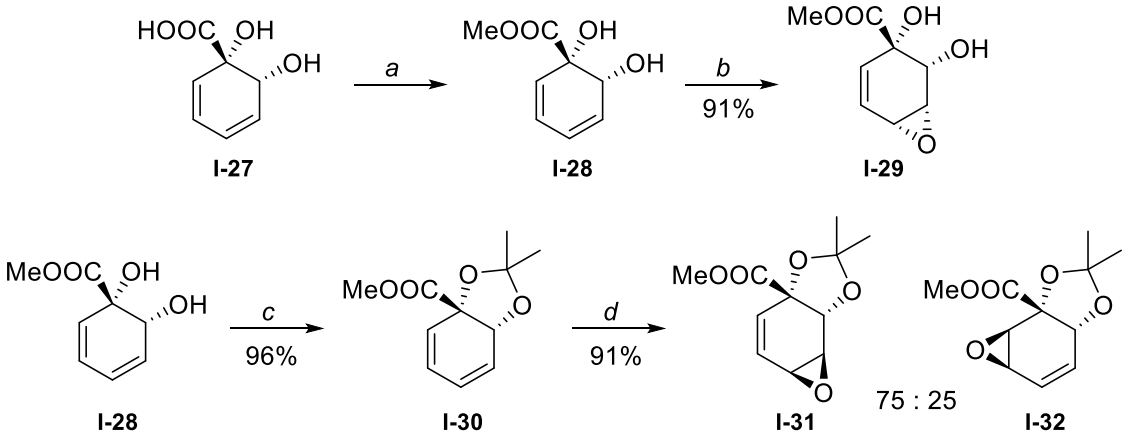


Figure I-03: Illustration of possible reactions that may be performed on arene diol **I-27**, taken from a review paper by Lewis.[57]

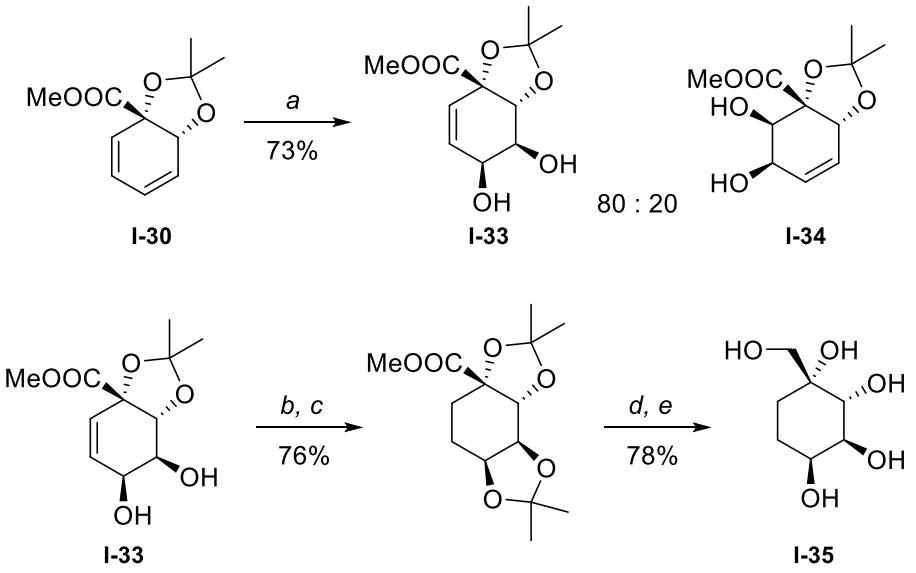
In 2001, Myers demonstrated the versatility of arene diol **I-27** through the synthesis of a range of highly functionalised, enantiopure molecules, focussing on oxidative and rearrangement chemistry.[58] Myers also showed that, when functionalising derivatives of arene diol **I-27**, the diastereo- and regio-selectivity could be controlled through making subtle modifications to the substrate. For example, epoxide **I-29** was produced as the sole product in the epoxidation of diene **I-28** with *m*CPBA, whereas in the epoxidation of acetonide protected diene **I-30**, the stereoisomeric epoxide **I-31** predominated as the major product, with a minor quantity of its regioisomer **I-32** also being formed (scheme I-17). Myers further reported the synthesis of several lactones, whose syntheses are detailed in the introduction to chapter 2, "Synthesis of enantiopure heterocycles from an arene *ipso,ortho*-diol". The strategies devised by Myers for controlling the diastereoselectivity of reactions on arene *ipso,ortho*-diols have subsequently been employed by multiple groups in the synthesis enantiopure compounds from arene diol **I-27**.



Scheme I-17: Epoxidation of dienes **I-28** and **I-30** as reported by Myers.[58] *a*) CH_2N_2, Et_2O, 0°C. *b*) *m*CPBA, CH_2Cl_2, RT. *c*) *p*TSA, 2,2-DMP, acetone, RT. *d*) *m*CPBA, CH_2Cl_2, RT.

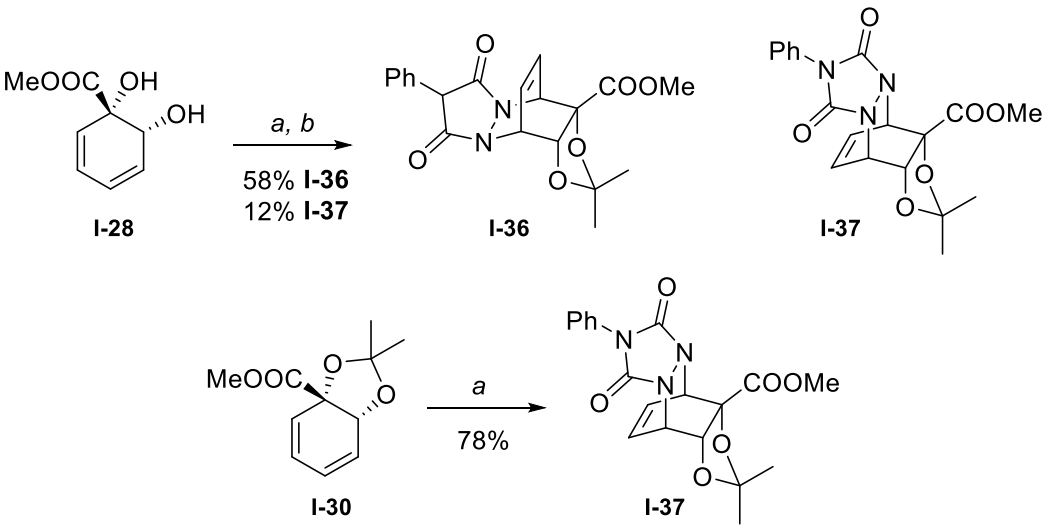
Cyclitols – carbocyclic rings bearing multiple hydroxyl groups – are known to possess a diverse range of biological activities.[33-35] In Parker's 2004 synthesis of the cyclitol carba-β-L-fructopyranose, an

acetonide group was employed to control the diastereoselectivity of dihydroxylation. Dihydroxylation of diene **I-30** afforded regioisomeric diols **I-33** and **I-34**, which were separable by column chromatography (scheme I-18). Further transformations afforded carba-β-L-fructopyranose in 7 steps from arene diol **I-35**.



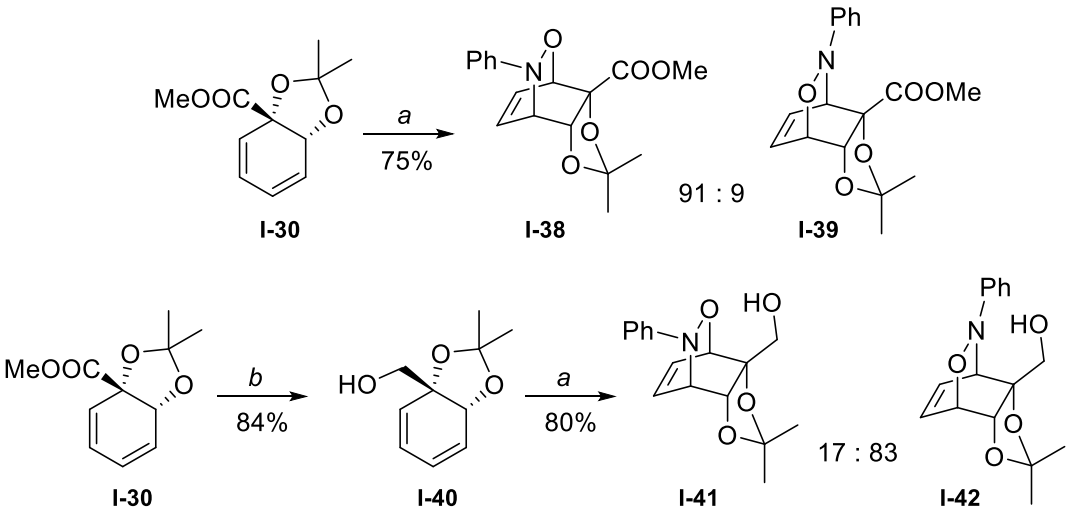
Scheme I-18: Synthesis of carba-β-L-fructopyranose **I-36**. *a*) OsO_4, NMO, acetone, water, RT. *b*) H_2, Pd/C, EtOAc, RT. *c*) HCl, 2,2-DMP, acetone, RT. *d*) DIBAL-H, THF, 0°C to RT. *e*) TFA, water, RT.

Widdowson reported the first intermolecular Diels–Alder reactions on an arene *ipso,ortho*-diol derived diene in 1995.[59] Widdowson found that the diastereoselectivity of cycloadditions on such dienes could also be controlled through modification of the diol. When reacting diene **I-28** with PTAD, a mixture of 2 products were formed which were inseparable by column chromatography (scheme I-19). Acetonide protection of the mixture provided diastereomers which were separable, allowing characterisation of the major product as **I-36**. Conversely, upon reacting diene **I-30** with PTAD, cycloadduct **I-37** was formed exclusively (scheme I-19). Protecting the diol as an acetonide group seemingly blocks attack of dienophiles from its residing face, allowing for diastereoselective cycloadditions to be performed.



Scheme I-19: Diels–Alder reaction between dienes **I-28** and **I-30** and PTAD.[59] *a*) PTAD, acetone, RT. *b*) *p*TSA, 2,2-DMP, RT.

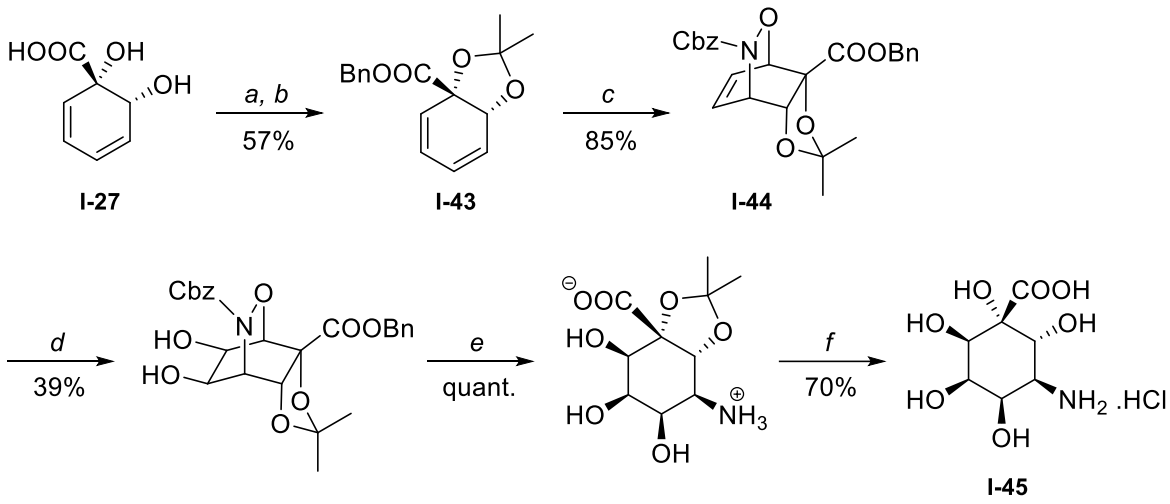
Widdowson also tested nitrosobenzene as a dienophile, which introduced the issue of regioselectivity in its cycloaddition with diene **I-30** and **I-40** (scheme I-20).[59] Widdowson suggested that steric effects between the incipient PTAD group and methyl ester could impart a degree of regioselectivity on this cycloaddition reaction, resulting in **I-38** forming as the major product. In contrast to this, the opposite regioselectivity could be induced through converting the methyl ester to a primary alcohol prior to exposing it to nitrosobenzene, providing **I-42** as the major product.



Scheme I-20: Diels–Alder reaction of dienes **I-30** and **I-40** with nitrosobenzene.[59] *a*) ONPh, toluene, RT. *b*) $LiAlH_4$, Et_2O, 0°C to RT.

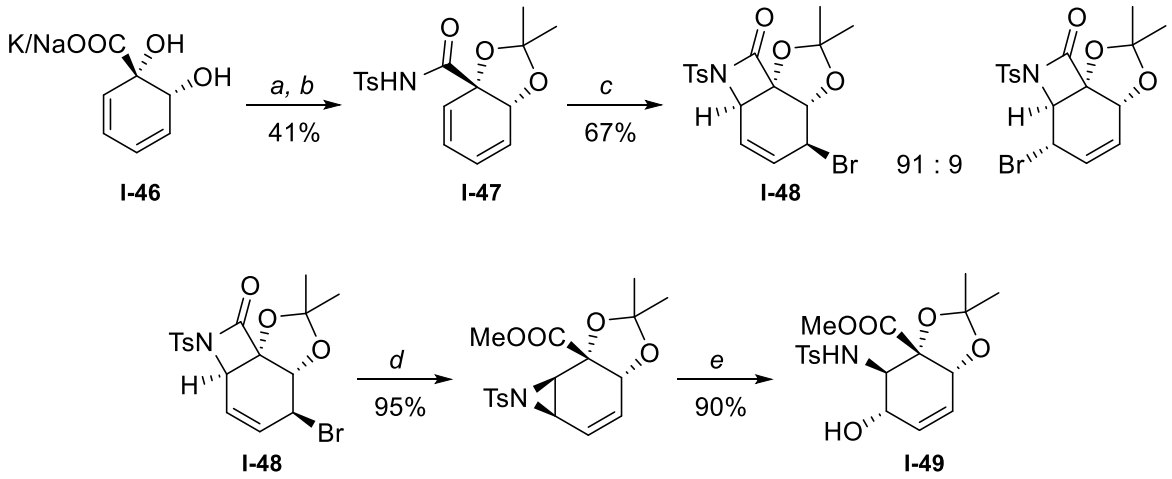
The Diels–Alder chemistry of arene *ipso,ortho*-diol derived dienes has subsequently been utilised by Lewis *et al.* in the synthesis of several enantiopure, poly-functionalised carbocycles.[60-63] In 2011, Lewis reported the synthesis of two inosaminoacids, from arene diol **I-27**, using a Diels–Alder reaction between diene **I-43** and benzyl *N*-hydroxycarbamate (oxidised *in situ* to form an acylnitroso dienophile)

to install an amine group onto the carbocyclic framework (scheme I-21).[60] Following further functionalisation, inosaminoacid **I-45** was synthesised. Enantiopure inosaminoacids are of interest in peptide chemistry, since the incorporation of cyclic amino acids into peptide chains can impart changes in a peptide's secondary structure.[64, 65] Aminocyclitols have also been synthesised by Lewis through a similar strategy.[62]



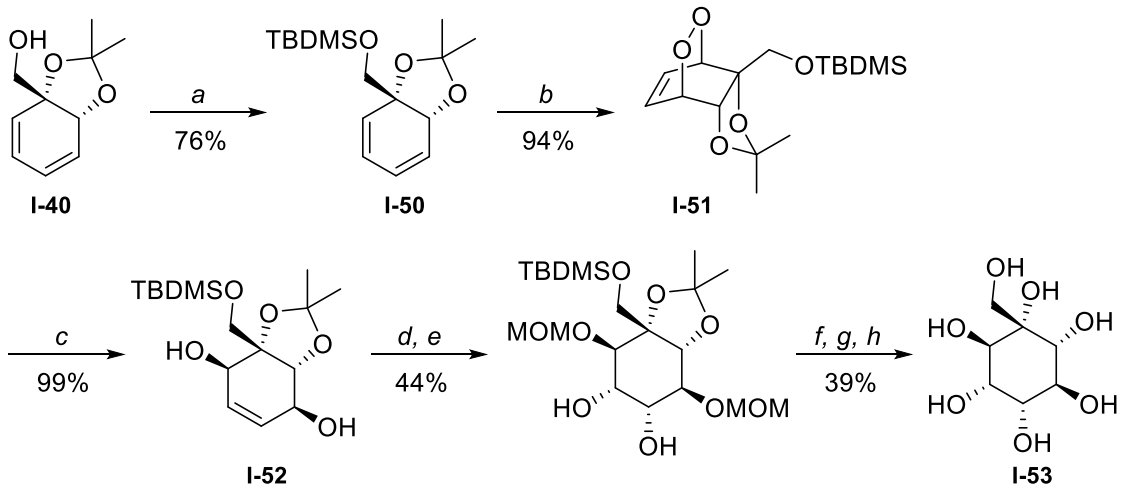
Scheme I-21: Synthesis of inosaminoacid **I-45** from arene diol **I-27**.[60] *a*) *p*TSA, 2,2-DMP, acetone, RT. *b*) BnBr, NEt_3, DMF, RT. *c*) Bu_4NIO_4, benzyl *N*-hydroxycarbamate, CH_2Cl_2, -78°C. *d*) OsO_4, NMO, acetone, water, RT. *e*) H_2, Pd/C, MeOH, RT. *f*) HCl, water, RT.

An alternative strategy for nitrogen incorporation onto the carbocyclic scaffold of arene *ipso,ortho*-diols was developed by Carrera in 2017.[66] Following the isolation of the mixed sodium/potassium salt arene diol **I-46**, acetonide protection was conducted followed by reaction with *para*-toluenesulfonyl isocyanate to give amide **I-47** (scheme I-22). Treating amide **I-47** with NBS afforded β-lactam **I-48** as the major product, which upon reaction with potassium cyanide followed by water gave β-sulfonamido-γ-hydroxyester **I-49.**



Scheme I-22: Carrera's synthesis of β-amino-γ-hydroxyester **I-49**.[66] *a*) TFA, 2,2-DMP, 0°C to RT. *b*) *p*TsNCO, NEt_3, THF, RT. *c*) NBS, $NaHCO_3$, MeCN, 0°C to RT. *d*) KCN, MeOH, DMF, RT. *e*) $NaHSO_3$, acetone, water, 75°C.

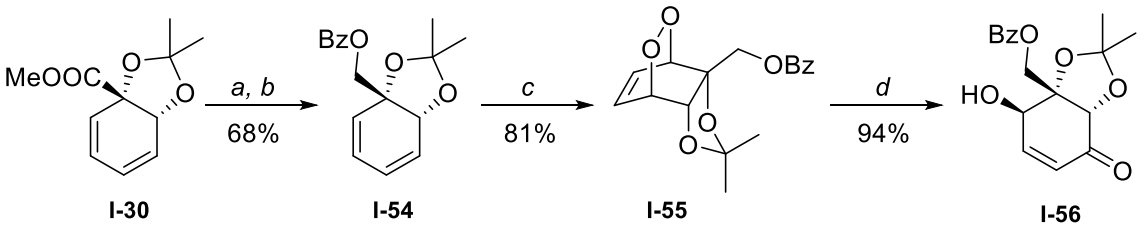
The diverse biological activity of cyclitols has also prompted Lewis to investigate their synthesis from arene *ipso,ortho*-diol **I-27**.[33-35] A singlet oxygen cycloaddition was performed upon diene **I-50** by Lewis and co-workers for this purpose. After reductive cleavage of the resulting endoperoxide **I-51**, diol **I-52** was furnished, which was then elaborated to cyclitol **I-53** (scheme I-23).[63]



Scheme I-23: Synthesis of cyclitol **I-53** from diene **I-40**. *a*) TBDMSOTf, NEt_3, CH_2Cl_2, -78°C to RT. *b*) O_2, TPP, *hv*, CCl_4, 10°C. *c*) Thiourea, CH_2Cl_2, MeOH, RT. *d*) MOMCl, DIPEA, CH_2Cl_2, RT. *e*) OsO_4, NMO, acetone, water, RT. *f*) HCl, water, RT. *g*) Ac_2O, pyridine, 0°C. *h*) NH_3, MeOH, RT.

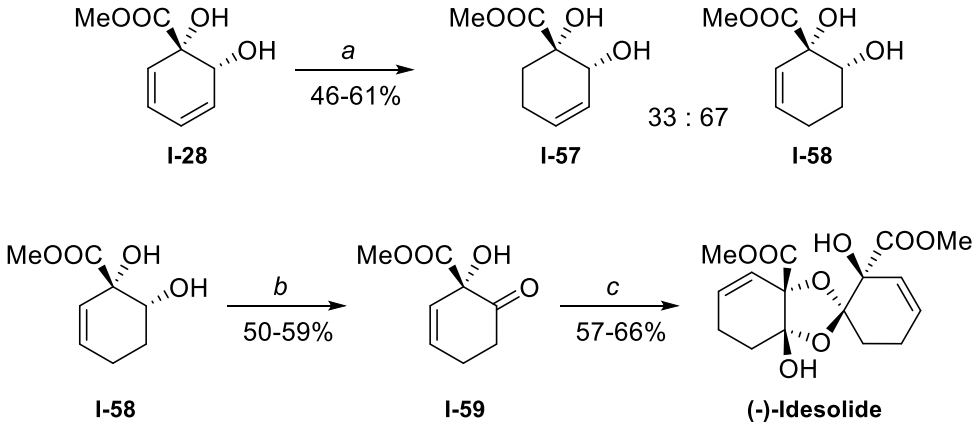
Lewis and co-workers also exploited singlet oxygen cyclo-addition chemistry in the synthesis of zeylenols and zeylenones.[61] Both enantiomers of zeylenol can be isolated from a variety of sources, such as *Uvaria zeylanica* and *Boesenbergia kaempferia,*[67, 68] however only (–)-zeylenone has been isolated from nature to date. Lewis conducted a Kornblum–DeLaMare rearrangement on endoperoxide **I-55** in an attempt to synthesise a (+)-zeylenone congener (scheme I-24). Whilst this route to a zeylenone was ultimately unsuccessful, it is a demonstration of how γ-hydroxyenones can

be easily synthesised from arene diol **I-27**. Instead, Lewis and co-workers found success in the synthesis of a zeylenone through a route that reductively cleaved the endoperoxide bridge of **I-55**. Lewis has also previously reported the synthesis of a (bis)epoxide from an arene diol derived endoperoxide.[63]



Scheme I-24: Kornblum–DeLaMare rearrangement of endoperoxide **I-55**. *a*) $LiBH_4$, THF, 0°C. *b*) BzCl, NEt_3, CH_2Cl_2, RT. *c*) O_2, TPP, *hv*, CCl_4, 10°C. *d*) DIPEA, CH_2Cl_2, RT.

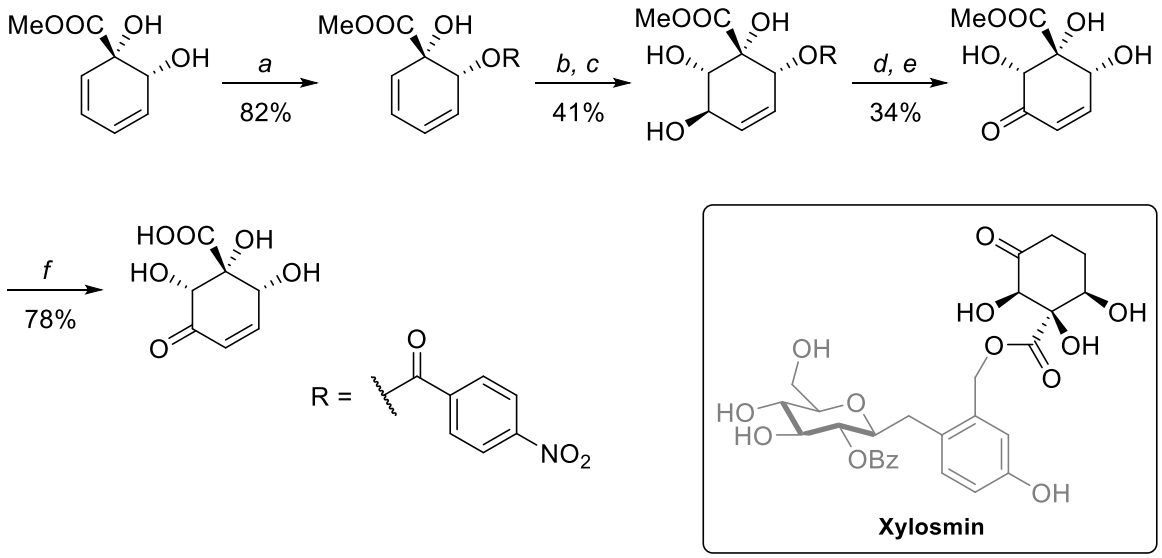
The synthesis of several other natural products from arene *ipso,ortho*-diols have also been reported over the previous decade. In 2011, Hudlický achieved the enantiopure synthesis of (–)-Idesolide from arene diol **I-27**.[69] (–)-Idesolide is known to possess potent anti-inflammatory activity, making its synthesis of interest to the scientific community.[70] Treating diene **I-28** with potassium azodicarboxylate and AcOH was found to effect the hydrogenation of only a single alkene of its diene, giving a mixture of alkenes **I-57** and **I-58** (scheme I-25). Subsequent oxidation of the secondary alcohol of **I-58** gave ketone **I-59**, which upon treatment with $NaHCO_3$ resulted in its dimerization to give (–)-Idesolide (scheme I-25).[69]



Scheme I-25: Hudlický's synthesis of (–)-Idesolide.[69] *a*) PAD, AcOH, MeOH, RT, 5°C. *b*) IBX, DMSO, RT. *c*) $NaHCO_3$, $CHCl_3$, RT.

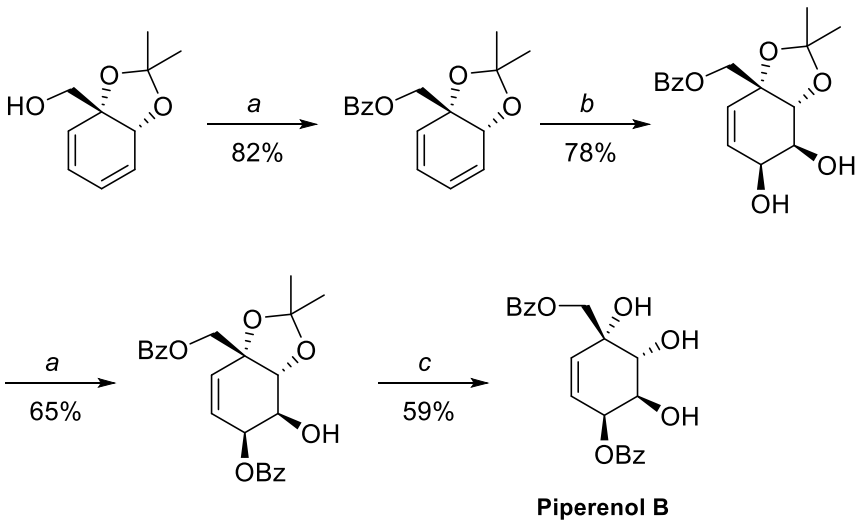
Hudlický has recently reported the synthesis of the hydroxylated cyclohexanone moiety of xylosmin from arene diol **I-27**.[71] Xylosmin is a natural product which, along with flacourtosides, can be found in extracts of *Flacoutia indica*. These extracts have been examined for their β-hematin inhibitory activity and as antimalarial agents.[72, 73] The potential biological activity of xylosmin has inspired interest in its

synthesis. Hudlický's enantioselective synthesis of the hydroxylated cyclohexanone moiety of xylosmin was completed in just 7 steps from arene *ipso,ortho*-diol **I-27** (scheme I-26).



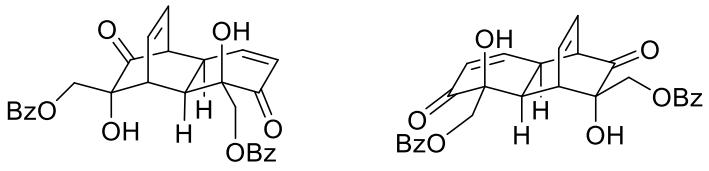
Scheme I-26: Structure of free hydroxyl derivative of xylosmin and Hudlický's synthesis of the cyclohexanone fragment of xylosmin.[71] *a*) *para*-nitrobenzoyl chloride, NEt_3, CH_2Cl_2, RT. *b*) *m*CPBA, CH_2Cl_2, RT. *c*) $Bi(OTf)_3$, MeCN, water, RT. *d*) DDQ, dioxane, 85°C. *e*) K_2CO_3, MeOH, RT. *f*) K_2CO_3, water, RT.

Piper cubeb and *Uvaria rufa* extracts have been shown to contain several polyoxygenated compounds which possess a range of biological activities, including anti-leukemic and anti-tumour activities.[74, 75] Found in extracts of *Piper cubeb,* Piperenol B is a polyoxygenated cyclohexene that was targeted for synthesis by Mihovilovic in 2015.[76, 77] Not only did Mihovilovic achieve the synthesis of Piperenol B in 8 steps from benzoic acid (scheme I-27), the synthesis unambiguously confirmed the stereochemistry of Piperenol B found in extracts of *Piper cubeb*.



Scheme I-27: Mihovilovic's synthesis of Piperenol B.[76] *a*) BzCl, NEt_3, Et_2O, 0°C to RT. *b*) OsO_4, NMO, acetone, water, RT. *c*) HCl, THF, 40°C.

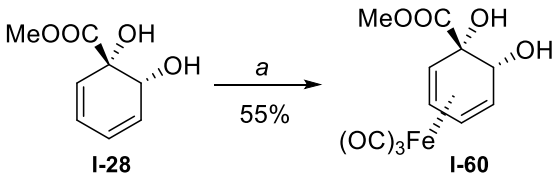
First isolated from *Uvaria grandiflora* in 1997, (–)-grandifloracin has been found to be cytotoxic against pancreatic cancer cells (figure I-04).[78] Later, in 2012, Awale established the enantiomeric (+)-grandifloracin to be an anti-austerity agent against human pancreatic cancer cell lines.[18] Due to the biological activity of grandifloracin, Quideau and Stoltz have both reported its racemic synthesis from inexpensive, aromatic starting materials.[16, 17] Lewis and co-workers have achieved the enantioselective total synthesis of (+)-grandifloracin from arene *ipso,ortho*-diol **I-21**,[79] utilizing a strategy which employs iron complexation chemistry that had been previously developed in the group.[80, 81]



(+)-Grandifloracin **(-)-Grandifloracin**

Figure I-04: Structures of (+)- and (–)-grandifloracin.

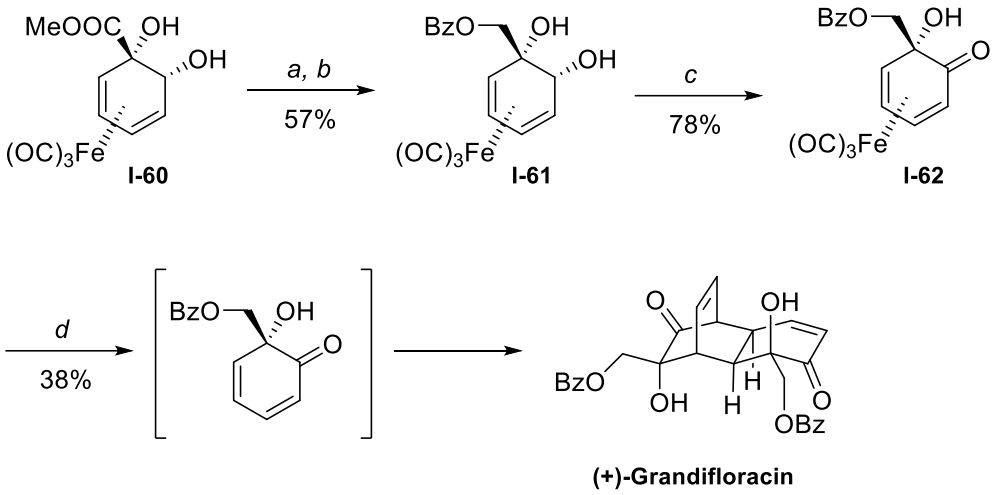
In 1958, Pauson reported the first example of a tricarbonyl(cyclohexadiene)iron complex.[82] In 2010, Lewis demonstrated that, when reacting arene diol **I-28** with nonacarbonyldiiron, a similar tricarbonyl(cyclohexadiene)iron complex could be accessed (scheme I-28).[81] The product of the reaction of arene diol **I-28** with nonacarbonyldiiron gave an enantiomerically pure product, which was shown to be **I-60** by X-ray crystallography. The observed selectivity seemingly arises as a result of the *cis*-diol directing coordination of the iron to the *back* face of the diene.



I-28 **I-60**

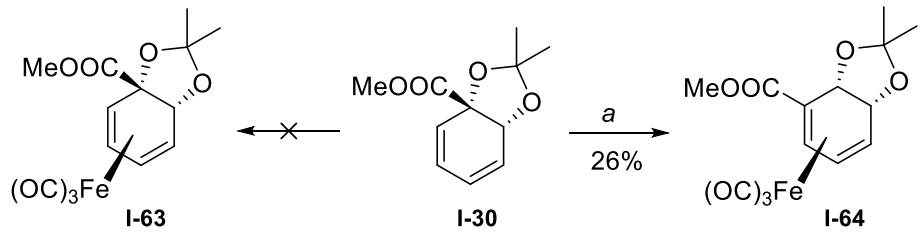
Scheme I-28: Synthesis of tricarbonyl(cyclohexadiene)iron complex **I-60**.[80] *a*) $Fe_2(CO)_9$, THF, RT.

Following complexation of diene **I-28** to iron, iron complex **I-60** can be treated with DIBAL-H and the resulting alcohol benzoylated to give **I-61** (scheme I-29).[83] Subsequent oxidation of the secondary alcohol using manganese dioxide then gave iron bound dienone **I-62** (scheme I-29). Upon de-complexation of iron, spontaneous dimerization occurs furnishing (+)-grandifloracin (scheme I-29). This is the first reported enantioselective synthesis of (+)-grandifloracin.



Scheme I-29: Lewis' enantioselective synthesis of (+)-grandifloracin.[83] *a*) DIBAL-H, THF, CH_2Cl_2, -78°C to RT. *b*) BzCl, 2,4,6-collidine, THF, RT. *c*) MnO_2, CH_2Cl_2, RT. *d*) Ceric ammonium nitrate, acetone, 0°C.

Subsequent studies by Lewis and co-workers into the iron complexation chemistry of arene diols resulted in the discovery of a novel rearrangement reaction.[81] In an attempt to achieve iron complexation to the face of the diene *anti* to the diol, diol **I-28** was protected to give acetonide **I-30**. It was envisaged that iron complexation would then result in iron complex **I-63**. However, upon reaction of diene **I-30** with nonacarbonyldiiron, iron complex **I-64** was instead formed (scheme I-30). This discovery is noteworthy since it provides access to the opposite enantiomer to that obtained when synthesising arene *ortho,meta*-diols using TDO expressing bacteria. In addition to iron complexation chemistry of arene *ipso,ortho*-diols, Lewis has also investigated cobalt complexation chemistry.[84]



Scheme I-30: Rearrangement reaction of diene **I-30** when reacted with nonacarbonyldiiron.[81] *a*) $Fe_2(CO)_9$, THF, RT.

Research into the synthesis of enantiopure heterocycles from arene *ipso,ortho*-diols has been previously explored by several research groups.[58, 66, 85-87] A detailed account of this research can be found in the introduction to chapter 2, "Synthesis of enantiopure heterocycles from an arene *ipso,ortho*-diol". Likewise, a detailed account of the chemistry of substituted arene *ipso,ortho*-diols can be found in the introduction to chapter 4, "Exploiting a fluoro arene ipso,ortho-diol in synthesis".

The previous research into arene *ispo,ortho*-diols has demonstrated the great versatility of their use in synthesis, however there are a number of research areas that are yet to be exploited. At the outset of

this project, we aimed to to expand the known synthetic chemistry of arene *ipso,ortho*-diols through the synthesis asymmetric epoxidation organocatalysts and enantiopure heterocycles. In addition to these themes, the chemistry of fluoro arene *ipso,ortho*-diols was also to be investigated. Achieving these aims would greatly expand the known chemistry of arene *cis*-diols, whilst potentially offering access to compounds of chemical or biological utility.

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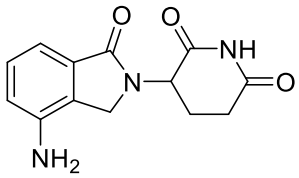
Synthesis of enantiopure heterocycles from an arene *ipso,ortho*-diol

Introduction to the synthesis of heterocycles from arene *ipso,ortho*-diols

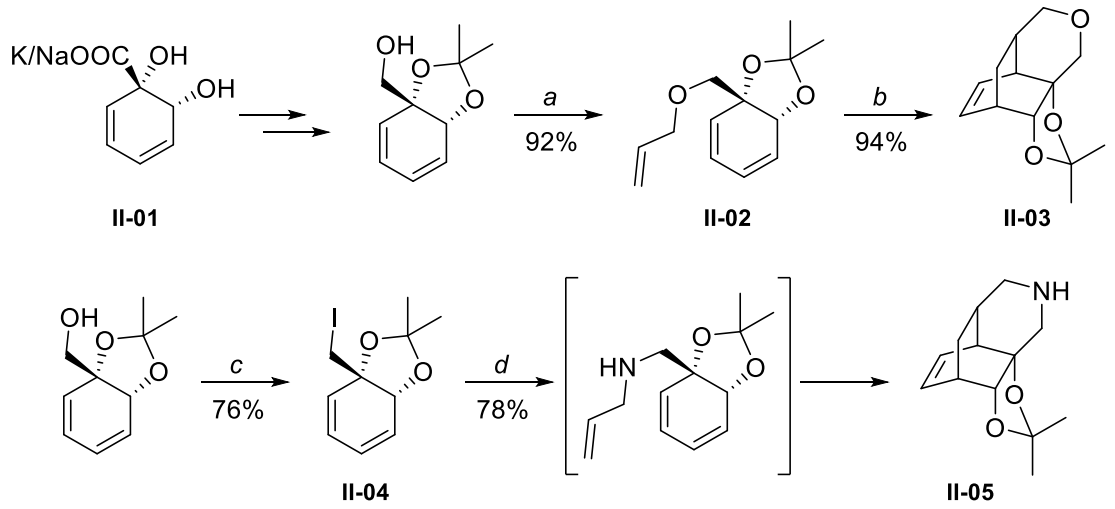
Heterocyclic compounds have found extensive use in agricultural chemicals and pharmaceuticals,[1, 2] with 80% of the best-selling small molecule drugs of 2010 containing at least 1 heterocycle.[3] Indeed, bi-heterocyclic Lenalidomide (figure II-01) was the best-selling small molecule pharmaceutical of 2017.[4] The utility of heterocycles demands new strategies be developed to synthesise novel heterocyclic compounds so that drug-like chemical space may be expanded.



Lenalidomide

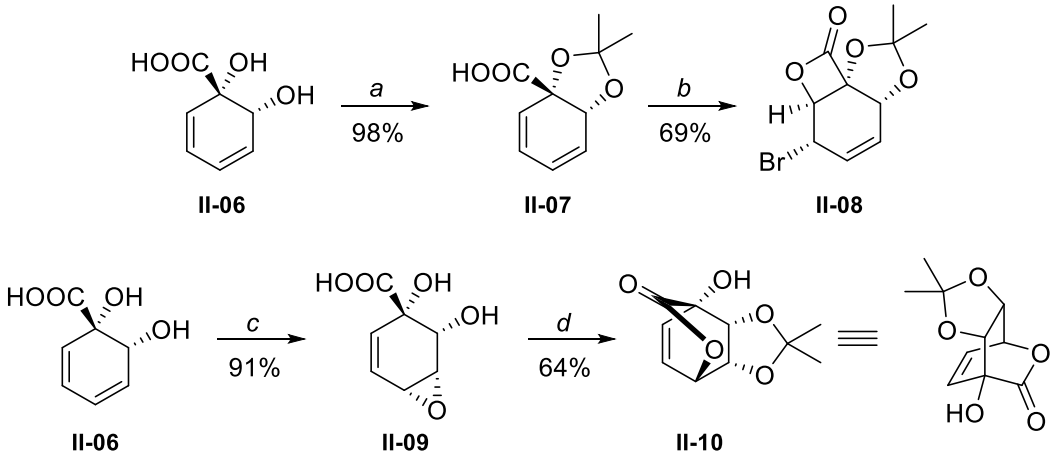
Figure II-01: Structure of lenalidomide (racemic), which is used in the treatment of multiple myeloma.[5]

The microbial oxidation of sodium benzoate using BZDO expressing organisms provides access to enantiopure arene diol **II-01**.[6, 7] Whilst arene diol has been used in the synthesis of a variety of carbocycles,[8-18] its use in the synthesis of heterocycles has been less extensively researched. Two examples of heterocycle synthesis from arene diol **II-01** were reported by Mihovilovic in 2004 using a strategy based on intra-molecular Diels–Alder reactions (scheme II-01).[19] Following the synthesis of diene **II-02**, cyclization was affected under microwave conditions to give poly-cyclic **II-03**, which contains an oxygen heterocycle. Mihovilovic also found that treating diene **II-04** with allyl amine at 120°C affected a one-pot amination and intra-molecular Diels–Alder reaction to give *N*-heterocyclic **II-05**.



Scheme II-01: Mihovilovic's synthesis of heterocycle containing compounds from arene diol **II-01**.[20] *a*) NaH, Bu_4NI, allyl bromide, THF, 0°C. *b*) Toluene, 135°C in microwave. *c*) PPh_3, imidazole, iodine, toluene, reflux. *d*) Allyl amine, 120°C.

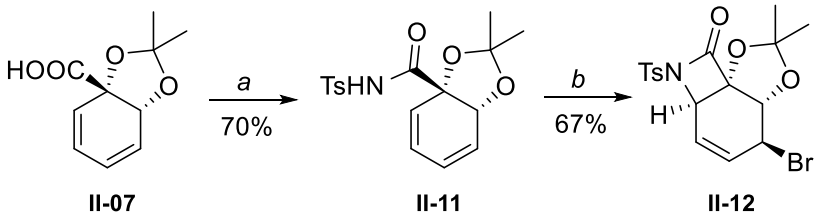
Myers has also reported the synthesis of 2 heterocycles from arene diol **II-06** (scheme II-02).[16] Acetonide protection of arene diol **II-06** afforded **II-07**. Upon treating diene **II-07** with NBS, formation of a bromonium ion on the most hindered alkene of diene **II-07** preceded nucleophilic attack of the proximal carboxylic acid on the bromonium ion, giving lactone **II-08**. Synthesis of lactone **II-10**, however, was achieved through initial epoxidation of arene diol **II-06** to give epoxide **II-09**. Refluxing **II-09** in perchloric acid and acetone affected the one-pot epoxide ring opening of **II-09**, through attack of the proximal carboxylic acid, followed by acetonide protection of the resulting diol to afford lactone **II-10**.



Scheme II-02: Myer's synthesis of lactones **II-08** and **II-10**.[16] *a*) *p*TSA, 2,2-DMP, acetone, RT. *b*) NBS, toluene, CH_2Cl_2, RT. *c*) *m*CPBA, EtOAc, RT. *d*) $HClO_4$, acetone, reflux.

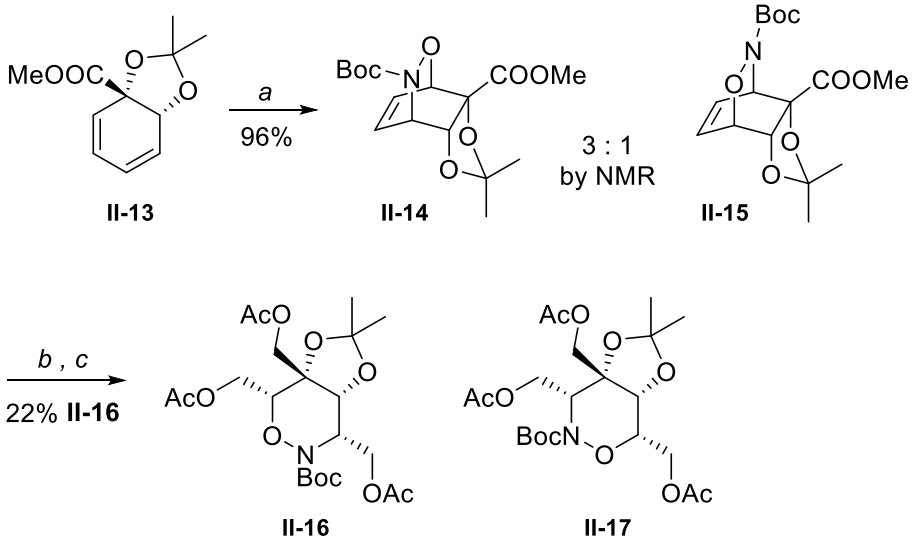
In 2017, Carrera reported the synthesis of a β-lactam from arene diol **II-12** (scheme II-03)[21] using a similar strategy to that used by Myers in the synthesis of lactone **II-08**.[16] In contrast to the research

done by Myers, however, intramolecular cyclisation to form β-lactam **II-12** proceeded through bromination of the least hindered alkene of diene **II-11**, followed my intramolecular conjugate addition of the amide to the resulting allylic bromonium ion. β-lactam **II-12** was further derivatised by Carrera to give several carbocycles bearing amine groups. Whilst Mihovilovic's, Myers' and Carrera's research do demonstrate the synthesis of heterocycles from arene diol **II-01**, none of these methods modify the original carbocyclic scaffold of the arene diol.



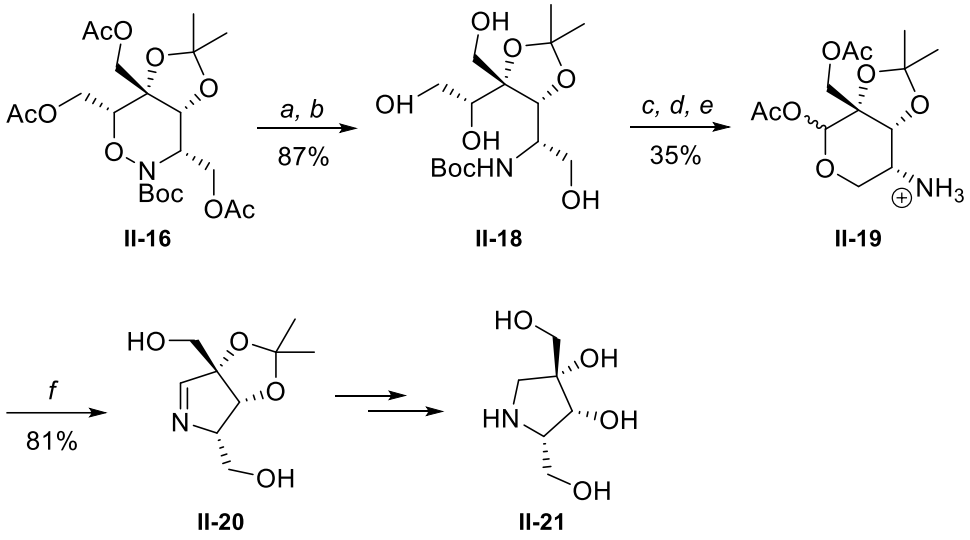
Scheme II-03: Carrera's synthesis of β-lactam **II-12**.[21] *a*) *p*TsNCO, NEt_3, THF, RT. *b*) $NaHCO_3$, NBS, MeCN, RT.

The only literature example demonstrating modification of the carbocyclic scaffold of arene diol **II-01** was reported by Hudlický in 2014 when synthesising a pyrrolidine.[22] After derivatising arene diol **II-01** as its acetonide protected methyl ester **II-13**, a cycloaddition reaction with an acylnitroso dienophile (generated *in situ*) was conducted to give inseparable regioisomers **II-14** and **II-15** (scheme II-04). A similar cycloaddition reaction had been previously reported by Lewis *et al*.[11] Reductive ozonoylsis of regioisomers **II-14** and **II-15** followed by acetylation of the resulting alcohols gave regioisomers **II-16** and **II-17** (scheme II-04). These regioisomers were separable by column chromatography, allowing **II-16** to be isolated in 22% yield. The isolated yield of **II-17** was not reported.



Scheme II-04: Initials synthetic steps in Hudlický's synthesis of a pyrrolidine.[22] *a*) $NaIO_4$, *t*-butyl hydroxycarbamate, MeOH, water, 0°C. *b*) O_3, CH_2Cl_2, $NaBH_4$, -70°C to RT. *c*) Ac_2O, DMAP, NEt_3, CH_2Cl_2, RT.

Deprotection of acetyl protected **II-16** was achieved with MeOH and K_2CO_3, after which reductive cleavage of the N-O bond was affected using $Mo(CO)_6$ providing acyclic **II-18** (scheme II-05).[22] $NaIO_4$ mediated glycol cleavage resulted in formation of a 6-membered lactol, which was protected to give **II-19** (scheme II-05). Reacting **II-19** with MeOH and K_2CO_3 resulted in lactol ring opening with subsequent ring closure through formation of imine **II-20** (scheme II-05). Further synthetic steps gave poly-hydroxylated pyrrolidine **II-21**. Whilst Hudlický's research demonstrates an ingenious route to pyrrolidine **II-21**, the number of synthetic steps required is significant.



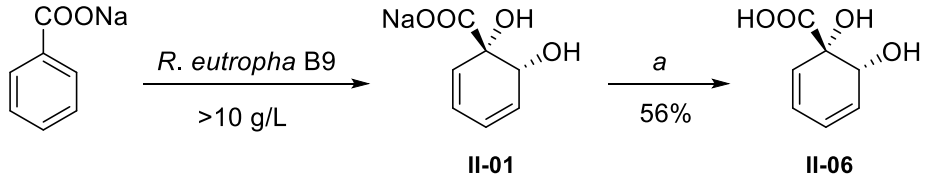
Scheme II-05: Final synthetic steps in Hudlický's synthesis of a pyrrolidine.[22] *a*) K_2CO_3, MeOH, RT. *b*) $Mo(CO)_6$, MeCN, water, RT to reflux. *c*) $NaIO_4$, CH_2Cl_2, RT. *d*) Ac_2O, DMAP, NEt_3, CH_2Cl_2, RT. *e*) TFA, CH_2Cl_2, 0°C to RT. *f*) K_2CO_3, MeOH, RT.

Having reviewed the literature in this field, it was considered of great importance to develop synthetic strategies that allow rapid access to a diverse range of enantiopure heterocycles from arene diol **II-01**. It was envisaged that achieving this would not only allow access to novel heterocyclic compounds which may exhibit function, but also increase understanding of the reactivity of arene diols more broadly.

Results and discussion

Since Reiner's seminal paper on the microbial oxidation of sodium benzoate (scheme II-07),[6] iterative improvements to the biotransformation procedure have been made by several research groups.[15, 16, 20] The procedure adopted in our research bears a high similarity to the most successful reported procedures, however a noteworthy difference can be found by comparison of the equipment used for the biotransformations. This research reports the microbial oxidation of sodium benzoate using non-specialist equipment, furnishing carboxylate **II-01**. This demonstrates how specialist bioreactors are not compulsory when conducting the microbial oxidation of sodium benzoate, highlighting the accessibility of this biotransformation to non-specialist research groups (although it should be acknowledged that substrate concentrations achieved when using bioreactors tend be improved by between 30% and 50%).

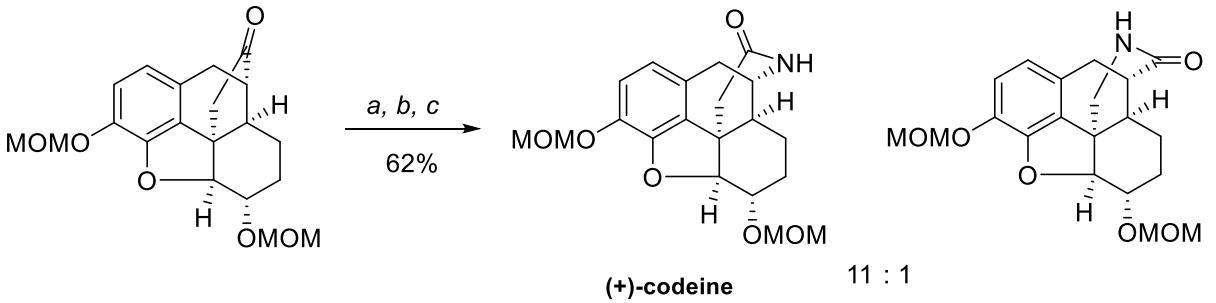
Carboxylate **II-01** has been used in the synthesis of various compounds, however there are several compounds that may only be accessed from its corresponding acid. As such, carboxylate **II-01** and acid **II-06** have both been synthesised and used as starting materials in the synthesis of enantiopure heterocycles (scheme II-06).



Scheme II-06: Microbial oxidation of sodium benzoate to afford carboxylate **II-01** and acid **II-06**. *a*) conc. aq. HCl, water, 0°C.

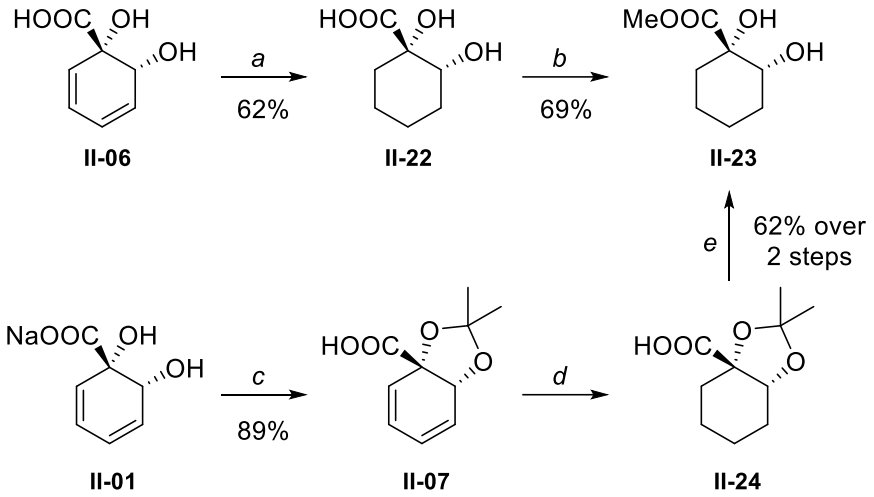
Attempted Beckmann rearrangement of an arene diol derived oxime

The Beckmann rearrangement, first reported by Beckmann in 1886,[23] allows the synthesis of amides from oximes, which themselves can be easily accessed from ketones. Since its discovery, the Beckmann rearrangement has found use in the industrial scale synthesis of ε-caprolactam[24] – used as a monomer in the synthesis of Nylon-6 – as well as in total synthesis. For example, the Beckmann rearrangement has been used in the synthesis of (+)-codeine (scheme II-07), a clinically used opiate.[25]



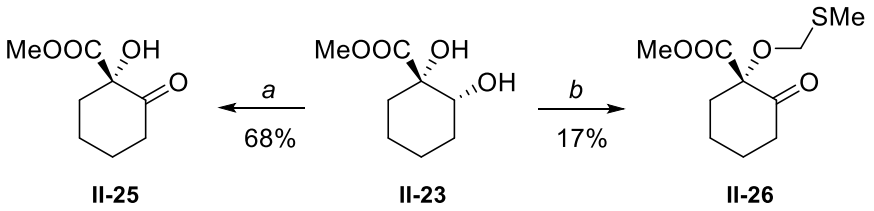
Scheme II-07: Beckmann rearrangement in the total synthesis of (+)-Codeine. *a*) $HONH_2$.HCl, NaOAc, MeOH. *b*) BsCl, triethylamine, DMAP, CH_2Cl_2. *c*) AcOH.

By exploiting the Beckmann rearrangement, we aimed to synthesise a novel, enantiopure lactam from arene diol **II-01**. As such, it was necessary to synthesise a ketone derived from arene diol **II-01**. Lewis *et al*. have previously reported the synthesis of saturated methyl ester **II-23**, which was achieved through hydrogenation of acid **II-06**, followed by methylation of the resulting carboxylic acid **II-22** using TMS-diazomethane (scheme II-08).[12] This method was utilised in the subsequently reported research to furnish methyl ester **II-23**, however it was also established that accessing this compound directly from carboxylate **II-01** may be preferential owing to the difficulties associated with isolating acid **II-06** (partial acid catalysed re-aromatisation of the arene diol is observed upon its acidification). The catalytic hydrogenation of carboxylate **II-01** using Pd/C and hydrogen gas was unsuccessful, so carboxylate **II-01** was first derivatised as its acetonide protected acid **II-07** through a procedure developed by Hudlický.[15] Hydrogenation of this compound then proceeded smoothly to give saturated acid **II-24**, which upon reaction with *p*TSA in MeOH resulted in one-pot acetonide group deprotection and methylation of the carboxylic acid (scheme II-08). The latter method resulted in the synthesis of saturated methyl ester **II-23** in 55% yield over 3 steps from carboxylate **II-01**, compared to a yield of 24% over 3 steps from carboxylate **II-01** for the former procedure.



Scheme II-08: Synthetic routes to saturated methyl ester **II-23**. *a*) H_2, Pd/C, MeOH, RT, 23 hours. *b*) TMS-diazomethane, MeOH, benzene, RT, 20 minutes. *c*) TFA (5 equiv.), 2,2-DMP, 0°C to RT, 24 hours. *d*) H_2, Pd/C, EtOAc, RT, 16 hours. *e*) *p*TSA (1 equiv.), MeOH, RT, 5 days.

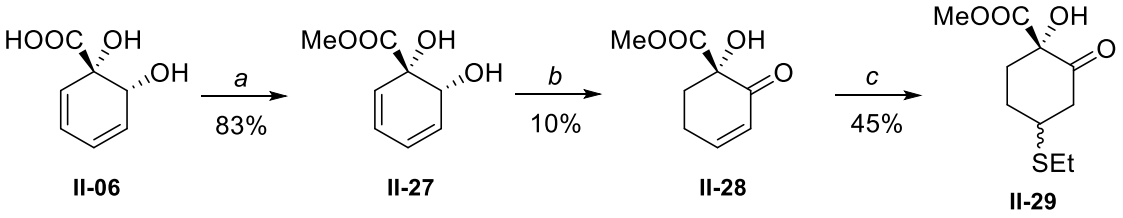
It was determined that oxidation of the secondary alcohol of **II-23** may result in a ketone which could be used in a Beckmann rearrangement reaction. Efforts were therefore made to oxidise this compound. Consistent with literature reports, it was found that Ley oxidation conditions resulted in glycol cleavage of diol **II-23**, which is also a known reaction of *cis*-diols when reacted with Dess–Martin periodinane.[26] However, reacting diol **II-23** with SIBX (stabilised IBX)[27] furnished the desired ketone **II-25** in a good yield (scheme II-09). Interestingly, it was also found that under Swern conditions oxidation of the secondary alcohol could only be achieved with simultaneous protection of the tertiary alcohol as its methyl-thioacetal, giving **II-26** (scheme II-09). The reason for the low yield of this reaction is unclear.



Scheme II-09: Oxidation of diol **II-23**. *a*) SIBX (2.0 equiv.), DMSO, 60°C, 3 hours. *b*) DMSO (2.0 equiv.), $(COCl)_2$ (1.0 equiv.), NEt_3 (5.0 equiv.), CH_2Cl_2, -78°C, 1 hour.

The synthesis of enone **II-28** was first reported by Hudlický in 2011,[14] which was achieved through the rearrangement of diene **II-27** catalysed by Grubbs' 1st generation olefin metathesis catalyst (scheme II-10).[28] This was thought to be a potential route to achieving the synthesis more highly substituted ketones that may be used in Beckmann type reactions. For this reason, Hudlický's work was replicated to give enone **II-28**. Whilst Hudlický and co-workers reported a yield of 45% for this reaction, replication of this yield proved challenging – in our hands, a maximum yield of just 10% could be

attained. The observed low yields were a result of thermal re-aromatisation of the starting material **II-27** under the reaction conditions. Grubbs' II catalyst and $RhCl_3.3H_2O$ were also tested as catalysts for this transformation. Grubbs' II catalyst provided enone **II-28** in a reduced yield (<3%), whereas $RhCl_3.3H_2O$ failed as a catalyst in this transformation.



II-06 **II-27** **II-28** **II-29**

Scheme II-10: Rearrangement of diene **II-27** to enone **II-28** and conjugate addition of ethanethiol to give **II-29**. *a*) TMS-diazomethane, MeOH, benzene, RT, 20 minutes. *b*) Grubbs' I catalyst (5 mol%), toluene, reflux, 18 hours. *c*) EtSH (1.1 equiv.), NEt_3, $CHCl_3$, 30°C, 22 hours.

Enone **II-28** was treated with ethanethiol and trimethylamine, resulting in the conjugate addition of ethanethiol to the enone (scheme II-10). The reaction was deemed to have succeeded due to the absence of any peaks indicative of an alkene in the ^{1}H NMR spectrum of the product, as well as the appearance of peaks characteristic of an ethyl chain. Unsurprisingly, this reaction produced a mix of both the *S,S* and *R,S* diastereomers of **II-29**. NMR analysis of the isomeric mixture of **II-29** was attempted with a view to establishing the relative ratio of each diastereomer in the mixture.

The presence of 2 overlapping singlets at δ = 3.80 and 3.79 ppm (H^{12}) in the ^{1}H NMR spectrum suggest that the methyl ester has been conserved during the thiolation reaction, as well as suggesting the presence of 2 diastereomers. Furthermore, the presence of a multiplet at δ = 1.30-1.20 ppm (H^{14}) in the ^{1}H NMR spectrum suggested the successful addition of ethanethiol to the enone. Using HSQC, peaks at δ = 14.9 and 14.7 ppm (C^{14}) could be assigned in the ^{13}C NMR spectrum, giving further confirmation of diastereomers. HMBC indicated an interaction of the multiplet at δ = 1.30-1.20 ppm (H^{14}) with the carbon peak at δ = 24.6 ppm (C^{15}) as well. HSQC allowed the assignment of the multiplet at δ = 2.62-2.49 ppm (H^{15}) as a result, which was confirmed by coupling interactions observed by COSY between the multiplet at δ = 1.30-1.20 ppm (H^{14}) and δ = 2.62-2.49 ppm (H^{15}). Due to the characteristic chemical shifts of carbonyls, the peak at δ = 204.5 ppm (C^5) was assigned as the ketone in both diastereomers. Peaks at δ = 171.2 and 170.1 ppm (C^9) in the ^{13}C spectrum were assigned as the ester carbonyls for each diastereomer. Carbon peaks at δ = 80.2 and 80.1 ppm (C^6) were assigned as the tetra-substituted carbon peaks for each diastereomer. These peaks suggest the conservation of key functional groups within **II-29**.

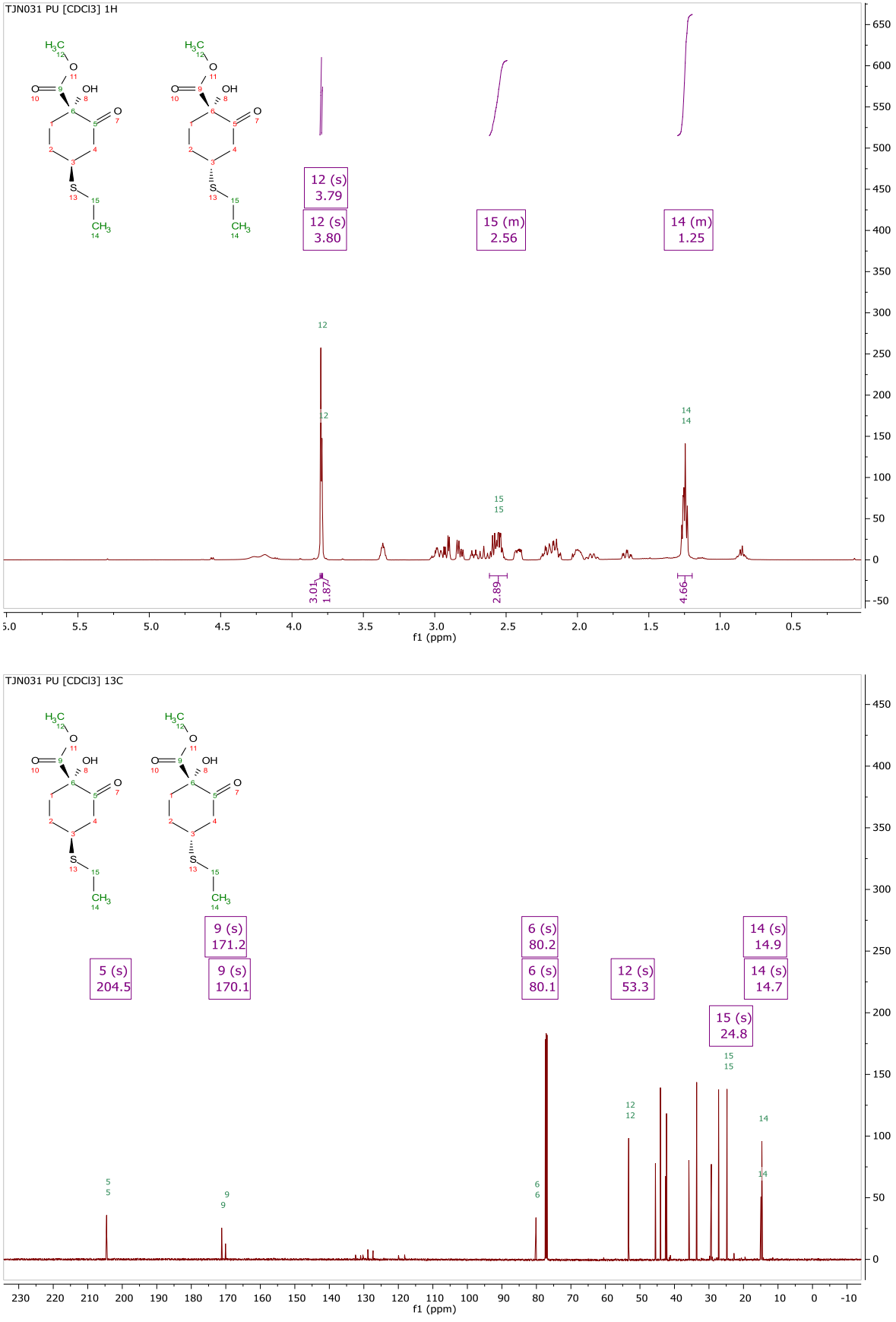
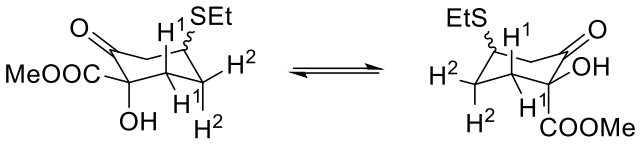


Figure II-02: ^{1}H NMR spectrum (top) and ^{13}C NMR spectrum (bottom) of mixture of diastereomers **II-29**.

Whilst assigning the methyl ester and ethanethiol peaks in the NMR spectra was relatively straightforward, assigning the ring protons and carbons for diastereomeric mixture **II-29** proved more challenging. This was due to a complicated ^{1}H spectrum arising from 7 different ring proton environments for each diastereomer, with each proton showing a complex splitting pattern.



Scheme II-11: Possible chair conformations for both diastereomers of **II-29**.

Consideration of the relative occupations of each possible chair conformation for diastereomers **II-29** (Scheme II-11) was not thought to be of importance in assigning ring protons H^1 and H^2. Assigning these protons would allow, by process of elimination, the peaks that are responsible for the remaining ring protons (H^3 and H^4) to be established.

For the major diastereomer (see figure II-03 for ^{1}H and ^{13}C NMR spectra), the carbon peak at δ = 171.2 ppm (C^9) shows a 3 bond HMBC interaction with 1 of the protons contributing to the multiplet at δ = 2.26-2.11 ppm (H^1). HSQC allowed the assigning of carbon peak δ = 33.6 ppm (C^1) and, as a result, of the ddd at δ = 2.42 ppm (C^1) in the ^{1}H NMR spectrum. The COSY spectra permitted assignment of multiplet δ = 2.04-1.95 ppm (H^2) in the ^{1}H NMR spectrum, whilst HSQC subsequently allowed assignment of carbon peak δ = 27.2 ppm (C^2) and of another of the protons contributing multiplet δ = 2.26-2.11 ppm (H^2).A similar strategy was employed when assigning the minor diastereomer's NMR spectra (see figure II-04 for ^{1}H and ^{13}C NMR spectra). A 3 bond HMBC interaction between this diastereomer's ester carbon at δ = 170.1 ppm (C^9) and proton td δ = 1.65 ppm (H^1) was observed, which subsequently allowed assignment of the carbon peak at δ = 35.8 ppm (C^1) and proton dt at δ = 2.73 ppm (H^1). COSY allowed the final proton contributing to the multiplet at δ = 2.26-2.11 ppm (H^2) to be assigned, followed by the carbon at δ = 29.3 ppm (C^2) and proton dddd at δ = 1.90 ppm (H^2).

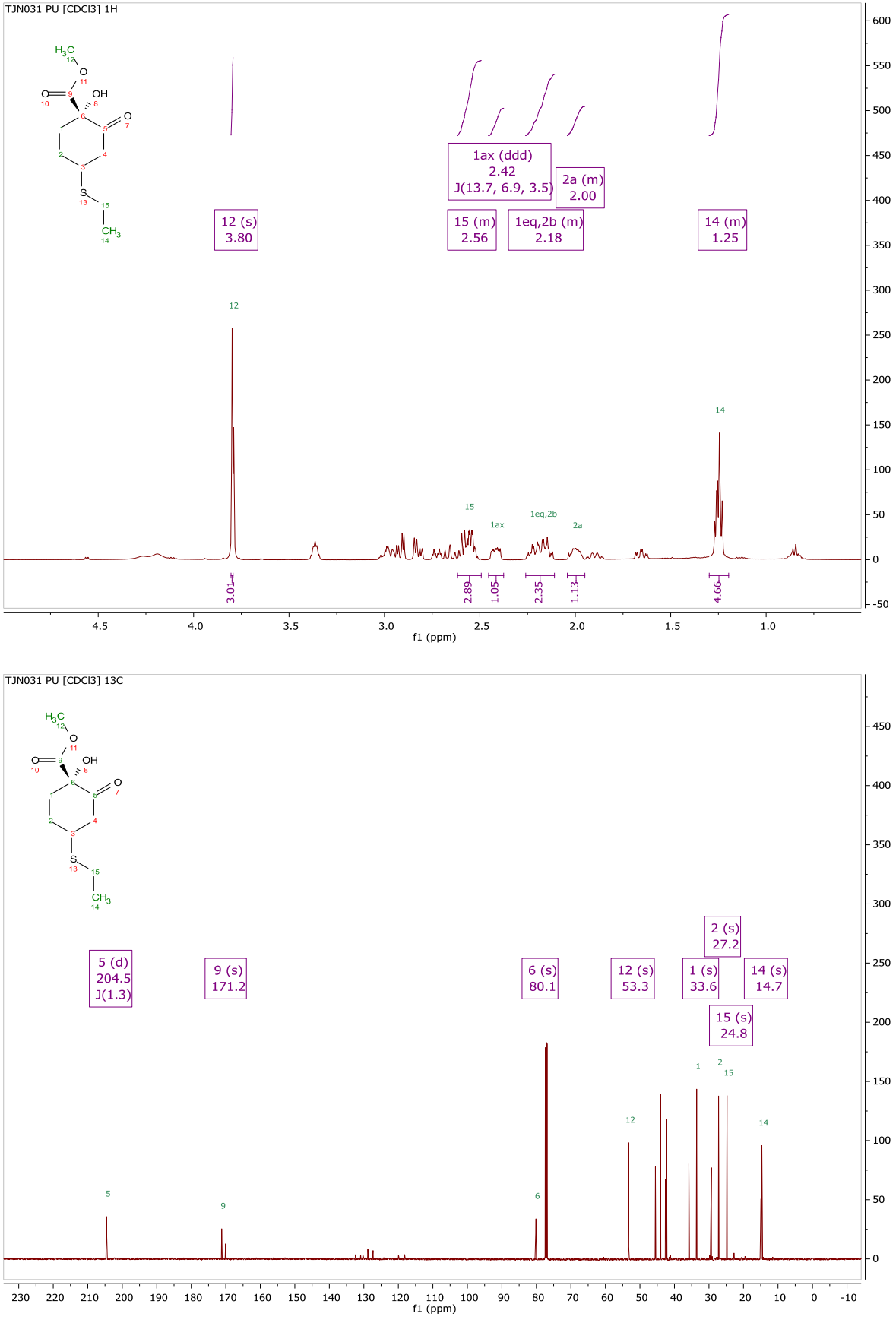


Figure II-03: ^{1}H NMR spectrum (top) and ^{13}C NMR spectrum (bottom) showing partial labelling of **II-29** major diastereomer.

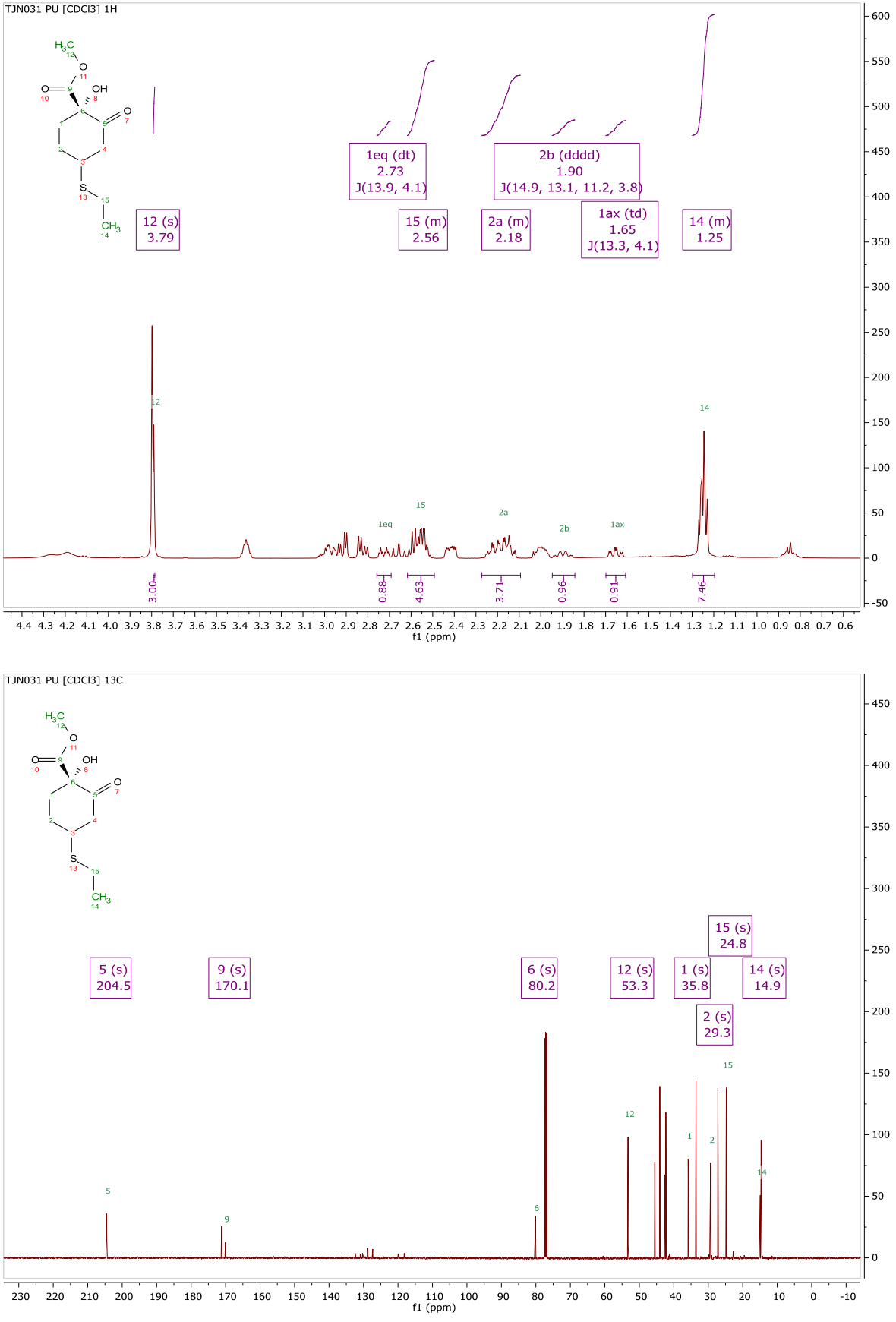
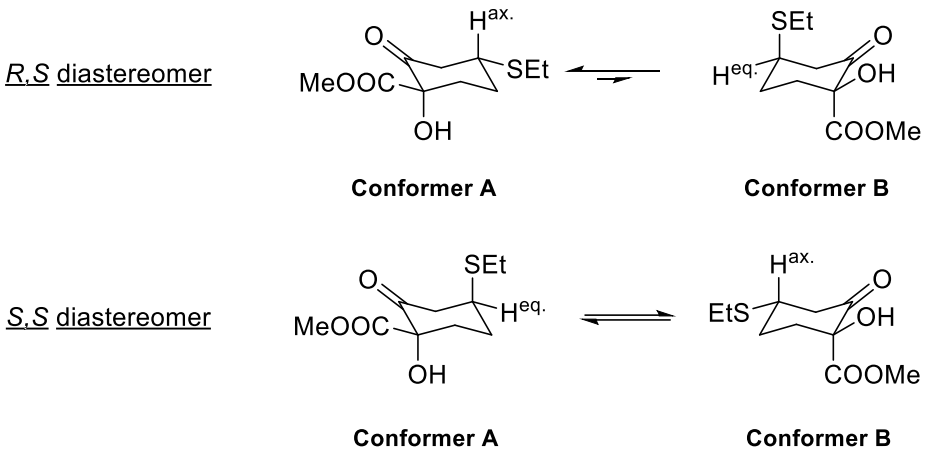


Figure II-04: ^{1}H NMR spectrum (top) and ^{13}C NMR spectrum (bottom) showing partial labelling of **II-29** minor diastereomer.

The Karplus equation states that coupling between vicinal protons is maximal when their dihedral angle is either 0° or 180°, with a minimum at 90°.[29] For this reason, it was envisaged that the observed J values for H^3 and H^4 in the ^1H NMR spectrum could be used to assign the stereochemistry of the major and minor components of the mixture of diastereomers **II-29**. In order to do this, however, it is first necessary to consider the possible chair conformations of each diastereomer (scheme II-16).

A values define the propensity of a substituent to preferentially adopt the equatorial position in a cyclohexane ring, with the magnitude of the A value being proportional to the steric bulk of the substituent.[30] In cyclohexane rings with multiple non-hydrogen substituents, a comparison of each substituent's A values can often provide valuable information on the preferred chair conformation adopted. Since there is no reported A value for a thioethyl group in the literature, instead the A value for a thiomethyl group was used in the comparison of A values in cyclohexane **II-29**. Reported A values for methyl ester, hydroxyl and thiomethyl groups are 1.31, 1.0 and 1.1 kcal/mol respectively.[31] Upon analysis of these A values, it was determined that the favoured chair conformation for the *R,S*-diastereomer **II-29** would place both the methyl ester and thioethyl group equatorial, with the hydroxyl group axial (conformer A, scheme II-12). However, the preferred chair conformer for the *S,S*-diastereomer **II-29** was less straightforward to establish due to the competing preference of the large methyl ester group to be equatorial versus both the hydroxyl and thiomethyl groups being equatorial.

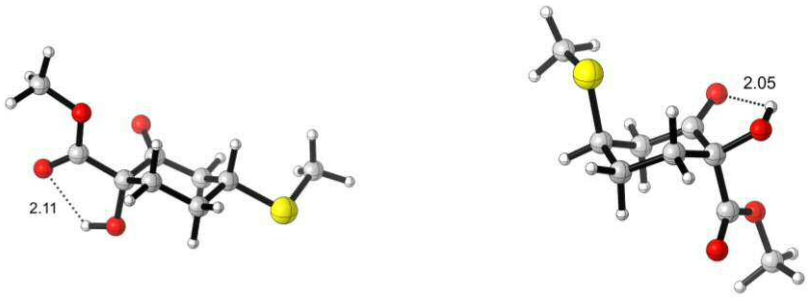


Scheme II-12: Predicted chair conformations for diastereomers **II-29** based on the reported A-values for each substituent.

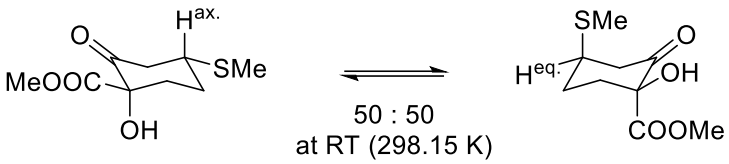
Computational modelling was conducted by Dr. Matthew Grayson (University of Bath) in order to unambiguously determine the preferred chair conformations for each diastereomer. DFT calculations were performed using Gaussian 16 (Revision A.03) to assess the relative free energies of the different conformers of the *R,S*- and *S,S*-diastereomers **II-29**.[32, 33] Contrary to the predictions made based on the substituents' A values, the energy difference between chair conformers A and B of the *R,S*-

diastereomer **II-29** was zero (scheme II-13). It is proposed that this is a result of a favourable hydrogen bond being established between the hydroxyl and ketone moieties in conformer B of the *R,S*-diastereomer which cannot be formed in conformer A, thus lowering the energy of conformer B relative to conformer A. This same interaction contributes to conformer B of the *S,S*-diastereomer being lower in energy than conformer A. With the relative energies of each conformer having been calculated, the ratio of each at RT (298.15 K) was calculated using the Gibb's free energy equation (scheme II-13).

As the computational investigation indicated that the ratio of conformers A and B for the *R,S*-diastereomer is 50:50 at RT and the ratio of conformers A and B of the *S,S*-diastereomer is 67:33 at RT, it was not possible to accurately assign stereochemistry of each component in the diastereomeric mixture based purely on its NMR spectra.



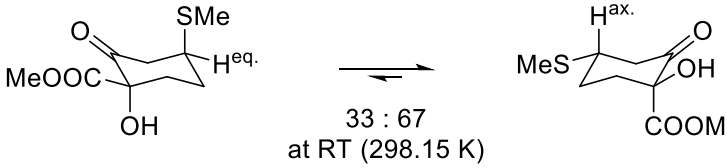
<u>*R*, *S* diastereomer</u>



Conformer A
ΔG = +1.2 kJ mol^{-1}

Conformer B
ΔG = +1.2 kJ mol^{-1}

<u>*S*, *S* diastereomer</u>



Conformer A
ΔG = +1.8 kJ mol^{-1}

Conformer B
ΔG = 0

Scheme II-13: Energies of each chair conformer for diastereomers of **II-29** as calculated by DFT (reported energies relative to chair conformer B for *S,S*-diastereomer).

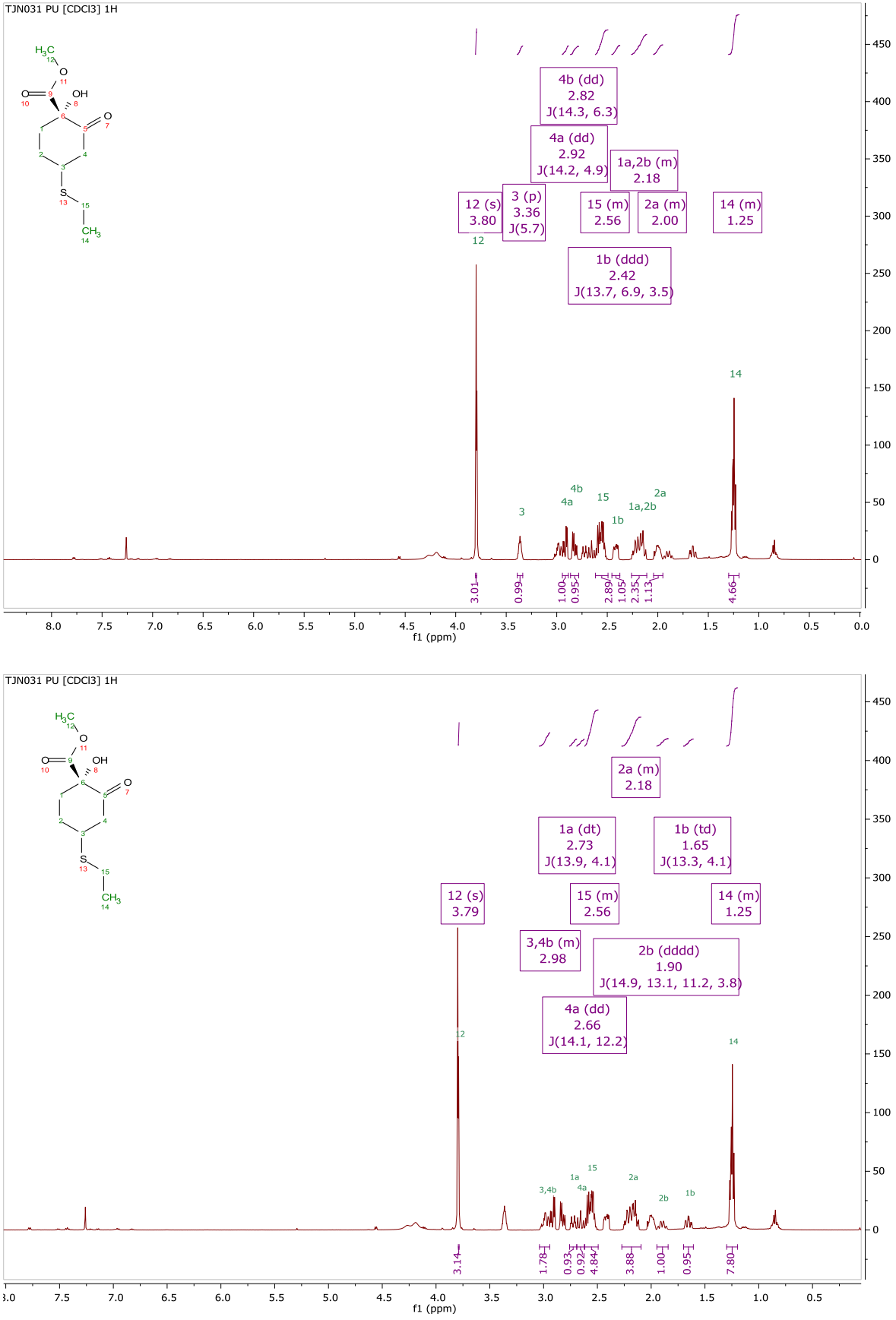
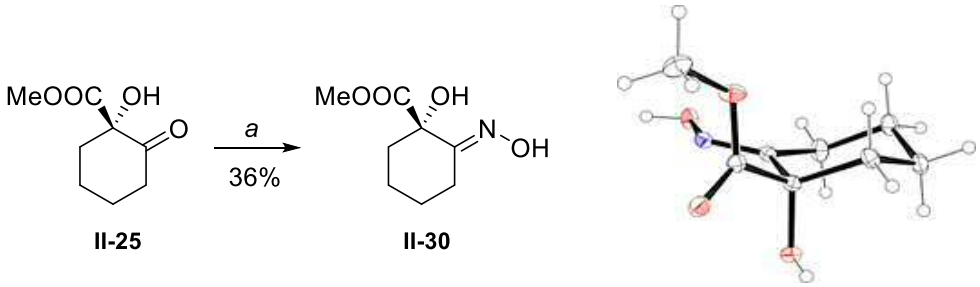


Figure II-05: ^{1}H spectrum of the major (top) and minor (bottom) diastereomer of **II-29** with complete labelling.

After complete assignment of the ^{1}H NMR spectra of each diastereomer in the isomeric mixture of **II-29** (figure II-05), it was nonetheless possible to determine the ratio of products using the relative integrals in the ^{1}H NMR spectrum. The ratio of major:minor products was thus calculated as 64:36, showing that the conjugate addition of ethanethiol to enone **II-28** proceeded with a minor degree of diastereocontrol.

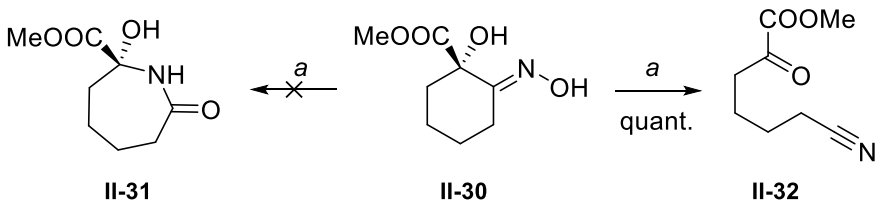
Despite a degree of selectivity being observed in the conjugate addition of ethanethiol to enone **II-28**, the low yielding route to the enone necessitates a more efficient isomerization reaction be developed in order to test more nucleophiles in this reaction. Since a degree of diastereoselectivity has already been observed, it may be expedient to examine how this selectivity changes when modifying the reaction conditions, substrate or nucleophile. Researching this topic more thoroughly could lead to a range of selective conjugate addition reactions to a microbially derived enone, providing the opportunity to synthesise multiple enantiopure, novel compounds.

With ketones **II-25** and **II-29** in hand, the synthesis of an oxime was attempted. The reaction of ketone **II-25** with hydroxylamine furnished oxime **II-30** in a yield of 36% (scheme II-14). The observed low yield could be a result of loss of product during recrystallisation, which may necessitate an improved method for purification of oxime **II-30** should it prove to be of value. ^{1}H NMR of the oxime suggested a single product was formed from this reaction, which was confirmed by X-ray crystallography to be the *E*-oxime. This was a desirable outcome, because successful Beckmann rearrangement of a geometrically pure oxime should theoretically be more likely to give rise to a single lactam product.



Scheme II-14: Synthesis of oxime **II-30** and its crystal structure. *a*) $HONH_2$.HCl (3 equiv.), NaOAc (10 equiv.), MeOH, RT, 16 hours.

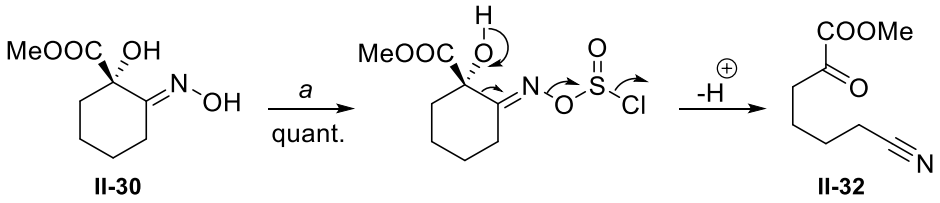
The Beckmann rearrangement of oxime **II-30** was subsequently attempted, with the aim of synthesising lactam **II-31**. It is reported in the literature that Beckmann rearrangement often fails when the oxime moiety is located α to a tetra-substituted carbon, however in most cases at least a minor quantity of lactam is formed.[34] In such cases, a competing Beckmann fragmentation also occurs, resulting in C-C bond cleavage and the formation of a nitrile as the major product. When reacting oxime **II-30** with thionyl chloride, this fragmentation occurred to give acyclic nitrile **II-32** exclusively (scheme II-15).



II-31 **II-30** **II-32**

Scheme II-15: Attempted Beckmann rearrangement of oxime **II-30**. *a*) thionyl chloride (10 equiv.), THF, 0°C, 3 hours.

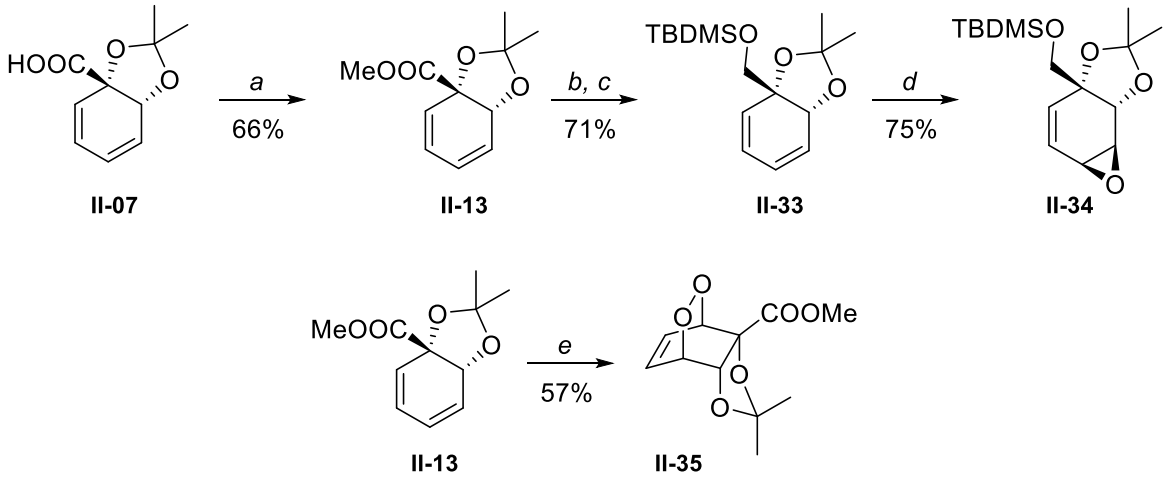
Indeed, a literature search of reactions that treat α-hydroxy oximes with thionyl chloride shows that Beckmann fragmentation occurs exclusively when exposing them to Beckmann rearrangement conditions.[35, 36] Based on the reported mechanism of Beckmann fragmentation, an argument can be made that these oximes may be yet more prone to fragmentation than their non-hydroxylated analogues. This is due to the alcohol – α to the oxime – promoting C-C bond cleavage through its deprotonation, resulting in formation of ketone **II-32** (scheme II-16).



II-30 **II-32**

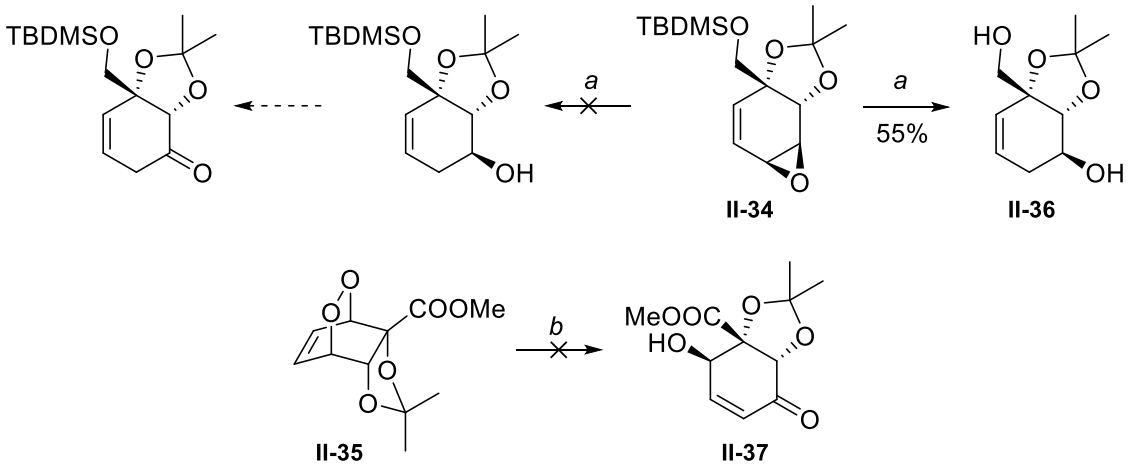
Scheme II-16: Proposed mechanism of Beckmann fragmentation of **II-30**. *a*) thionyl chloride (10 equiv.), THF, 0°C, 3 hours.

Due to Beckmann fragmentation, it was necessary to synthesise a ketone from arene diol **II-01** where the ketone moiety was not α to the tetra-substituted carbon. Two strategies were contrived to achieve this. The first was based on an epoxide ring opening reaction using a source of hydride and the second on the Kornblum–DeLaMare rearrangement of an *endo*-peroxide. As such, epoxide **II-34** and *endo*-peroxide **II-35** were synthesised (scheme II-17), with a view to using these compounds in the synthesis of ketones. The synthesis of endo-peroxides from arene diol **II-01** has been previously reported by Lewis *et al.*.[10, 12]



Scheme II-17: Synthesis of epoxide **II-34** and endoperoxide **II-35**. *a*) TMS-diazomethane, MeOH, benzene, RT, 20 minutes. *b*) $LiBH_4$ (2.0 equiv.), THF, 0°C to RT, 16 hours. *c*) TBDMSOTf (1.05 equiv.), NEt_3 (1.2 equiv.), CH_2Cl_2, -78°C to RT, 16 hours. *d*) *m*CPBA (1.4 equiv.), CH_2Cl_2, RT, 19 hours. *e*) O_2, TPP, CH_2Cl_2, 0°C, 8 hours.

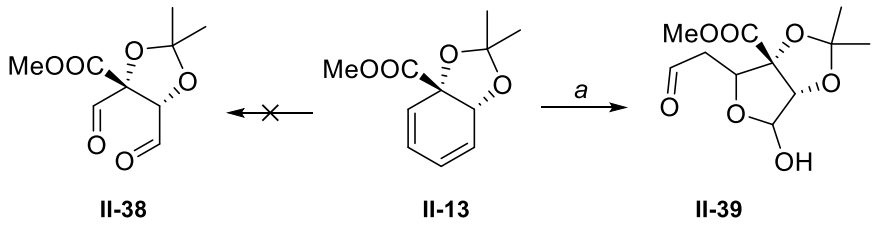
The reaction of epoxide **II-34** with $LiAlH_4$ did induce epoxide ring opening, however TBDMS deprotection was also observed to give diol **II-36** (scheme II-18). Epoxide ring opening was found to occur exclusively at C4, which can be rationalised through sterics (C3 is more sterically encumbered by the acetonide group than C4). TBDMS deprotection was an unexpected result, which prevented continued research into this strategy. Furthermore, Kornblum–DeLaMare rearrangement of endo-peroxide **II-35** to give derived γ-hydroxy-enone **II-37** was also unsuccessful (scheme II-18). Lewis *et al.* had previously reported the successful synthesis of similar γ-hydroxyenones, however it was also noted that difficulties were encountered due to the tendency of these γ-hydroxyenones to undergo a multitude of side reactions.[10] Careful modification of reaction conditions – for example reaction temperature, time or base – may have supressed unwanted side reactions, however this has not yet been studied. As such, research into the synthesis of a suitable ketone for Beckmann rearrangement is ongoing.



Scheme II-18: Epoxide opening of **II-34** and attempted Kornblum–DeLaMare rearrangement of endoperoxide **II-35**. *a*) $LiAlH_4$ (2.0 equiv.), THF, 0°C to RT, 16 hours. *b*) DIPEA, CH_2Cl_2, RT.

Synthesis of arene diol derived *O*-heterocycles

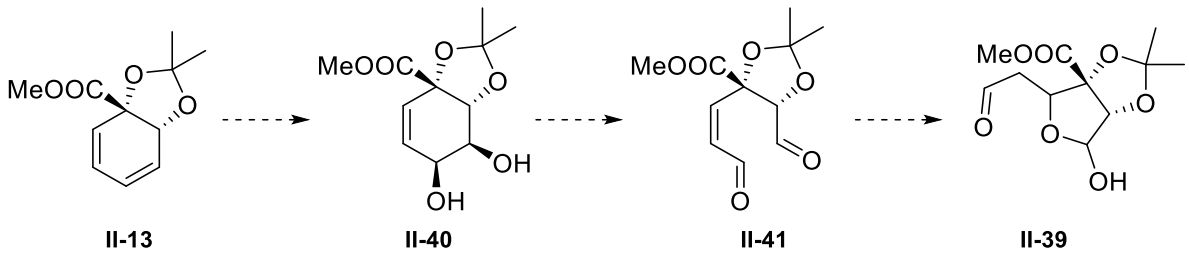
The microbial oxidation of sodium benzoate occurs regio- and enantio-selectively at the *ipso, ortho*-position of the aromatic ring, providing an enantiopure tetra-substituted carbon adjacent to a secondary alcohol. Due to the difficulties faced when synthesising chiral compounds, it was envisaged that this biotransformation could provide a chiral starting material that could be used in the synthesis of an array of enantiopure compounds. To achieve this, oxidative fragmentation of diene **II-13** was attempted in the hope of accessing dialdehyde **II-38**. This would then be examined for its suitability as a chiral starting material in synthesis. However, upon reaction of diene **II-13** with OsO_4 and $NaIO_4$ a product was obtained that contained a single aldehyde group (scheme II-19). This product was tentatively assigned as lactol **II-39**, which was unstable to column chromatography.



Scheme II-19: One step lactol formation from diene **II-13**. *a*) OsO_4 (5 mol%), $NaIO_4$ (2.0 equiv.), dioxane, water, RT, 16 hours.

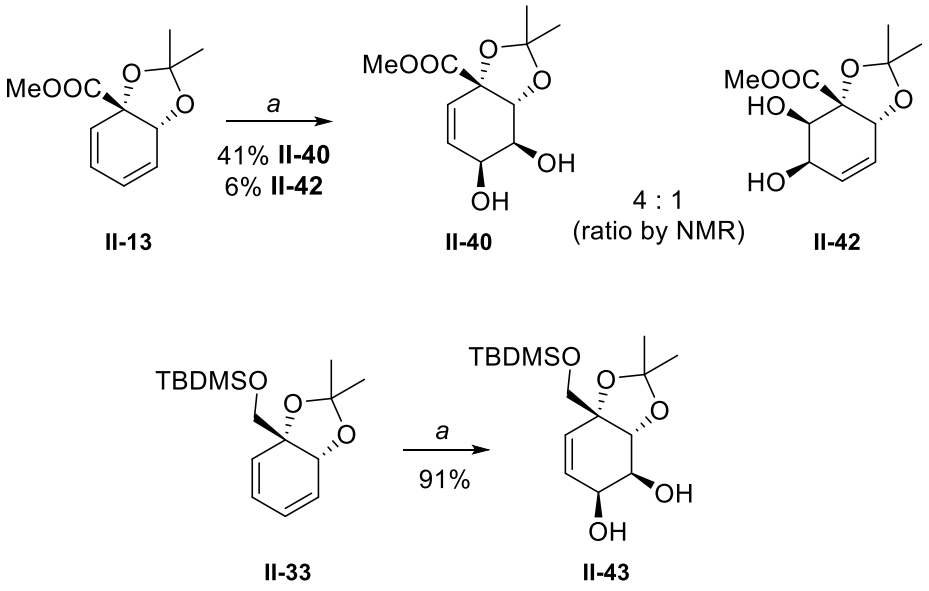
Proposed intermediates in the formation of lactol **II-39** are illustrated in scheme II-20. It was hypothesised that formation of diol **II-40** would initially occur, followed by rapid $NaIO_4$ mediated glycol cleavage to give ene-dialdehyde **II-41**. An intramolecular conjugate addition of the aldehyde to the enal then proceeds. It is suggested that at this stage of the reaction, a molecule of water is incorporated to form lactol **II-39**. The intermediates of this reaction pathway were targeted for

synthesis, as achieving this would not only help to confirm the proposed series of events, but also give access to ene-dialdehyde **II-41**, a molecule which possess a high degree of modifiable functionality.



Scheme II-20: Proposed intermediates in the formation of lactol **II-39** from diene **II-13**.

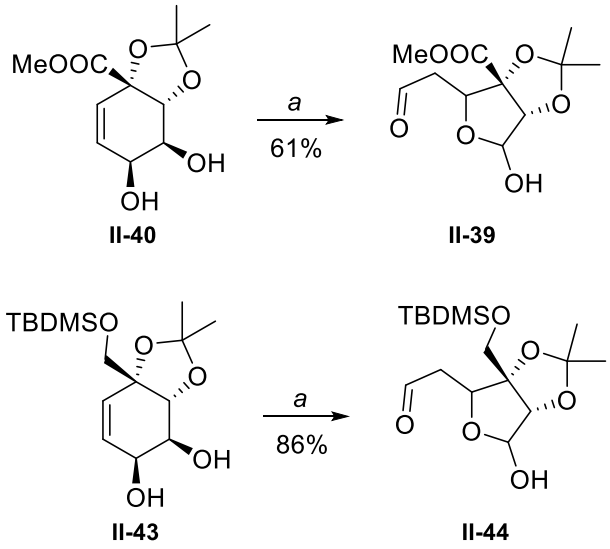
Synthesis of the diol proved straightforward. Parker *et al*. had previously reported the synthesis of regioisomeric diols **II-40** and **II-42** by treating diene **II-13** with OsO_4 and NMO.[17] Dihydroxylation favours the least hindered alkene in this reaction, however a mixture of regioisomers is still obtained (scheme II-21). Separation of this regioisomeric mixture by column chromatography was successful, albeit challenging. Conversely, dihydroxylation of the analogous TBDMS protected alcohol **II-33** proceeded regioselectively to give novel diol **II-43** exclusively (scheme II-21). The regioselectivity of this dihydroxylation reaction is confirmed by ^{1}H NMR, whereas the stereo-selectivity is assumed based on the stereoselectivity reported in the epoxidation and dihydroxylation of methyl ester **II-13**.[16, 17]



Scheme II-21: Dihydroxylation of dienes **II-13** and **II-33**. *a*) OsO_4 (2.5 mol%), NMO (1.2 equiv.), acetone, water, RT, 16 hours.

Reacting diols **II-40** and **II-43** with $NaIO_4$ in THF gave the desired enantiopure lactols in good to very good yields (scheme II-22). Furthermore, the products were obtained in remarkably good purity, thus avoiding the requirement for further purification. Lactols **II-39** and **II-44** could therefore be fully characterised and their identities confirmed. Despite the purity of lactols **II-39** and **II-44**, their

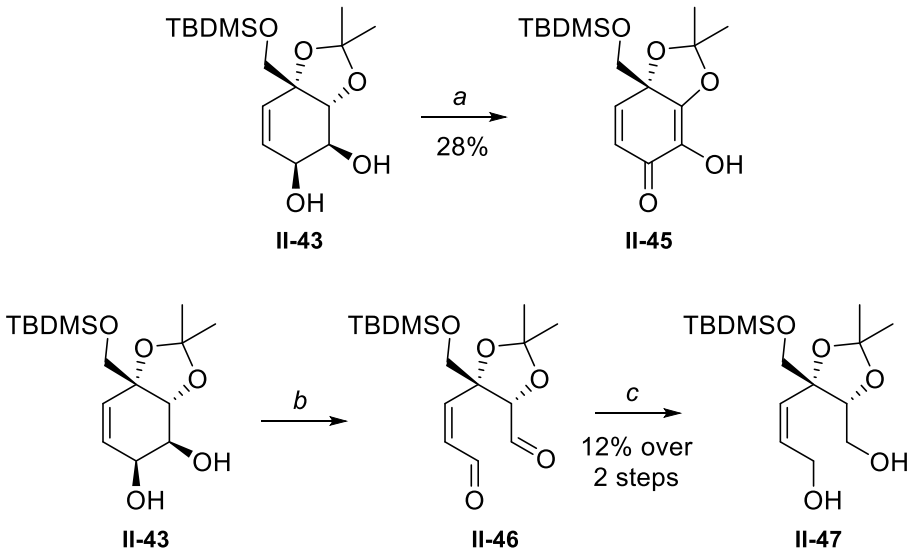
stereochemistry could not be fully established at this point, since the ^{1}H NMR spectra of these compounds provided insufficient information to ascertain it. To the best of our knowledge, this is the only example of the one-step synthesis of a lactol from an allylic diol. Only one other example of the reaction of an allylic diol with $NaIO_4$ is reported in the literature, which provides an uncyclized dialdehyde in 37% yield.[37] No explanation was offered by the authors for the apparent low yield.



II-40 **II-39** **II-43** **II-44**

Scheme II-22: Formation of lactols **II-39** and **II-44** from diols **II-40** and **II-43**. *a*) $NaIO_4$ (2.0 equiv.), THF, water, RT, 16 hours.

The dialdehyde intermediate inferred in the synthesis of lactols **II-39** and **II-44** proved more challenging to isolate. Because the dihydroxylation of TBDMS containing diene **II-33** proceeded regioselectively, diol **II-43** was chosen as a substrate for testing alternative oxidants to $NaIO_4$. Due to water being necessary for the formation of lactol **II-44**, conditions for glycol cleavage under an anhydrous environment were explored. Reaction of diol **II-43** with $Bu_4N.NaIO_4$ in anhydrous CH_2Cl_2 led to a complex mixture of products being formed. Contrastingly, reacting diol under Ley oxidation conditions furnished the unusual α-hydroxydiene-one **II-45**, with no glycol cleavage being observed (scheme II-23). In 2004, Koo *et al.* reported the glycol cleavage of similar allylic diols using $Pb(OAc)_4$, resulting in the formation of dialdehydes.[38] Diol **II-43** was therefore reacted with $Pb(OAc)_4$ for 50 minutes, furnishing a product with ^{1}H NMR signals that suggested the successful synthesis of dialdehyde **II-46** (figure II-05). Due to its instability, dialdehyde **II-46** was immediately reduced to acyclic diol **II-47** and fully characterised (scheme II-23). The low yield of diol **II-47** obtained is thought to be a result of the instability of intermediate dialdehyde **II-46**.



Scheme II-23: Attempted glycol cleavage reactions on **II-43**, eventually leading to the proposed dialdehyde intermediate **II-46** in the lactol forming reaction of **II-44**. *a*) TPAP (6 mol%), NMO (0.99 equiv.), CH_2Cl_2, RT, 3 hours. *b*) $Pb(OAc)_4$ (1.1 equiv.), MeCN, RT, 50 minutes. *c*) $NaBH_4$ (10 equiv.), MeOH, RT, 5 hours.

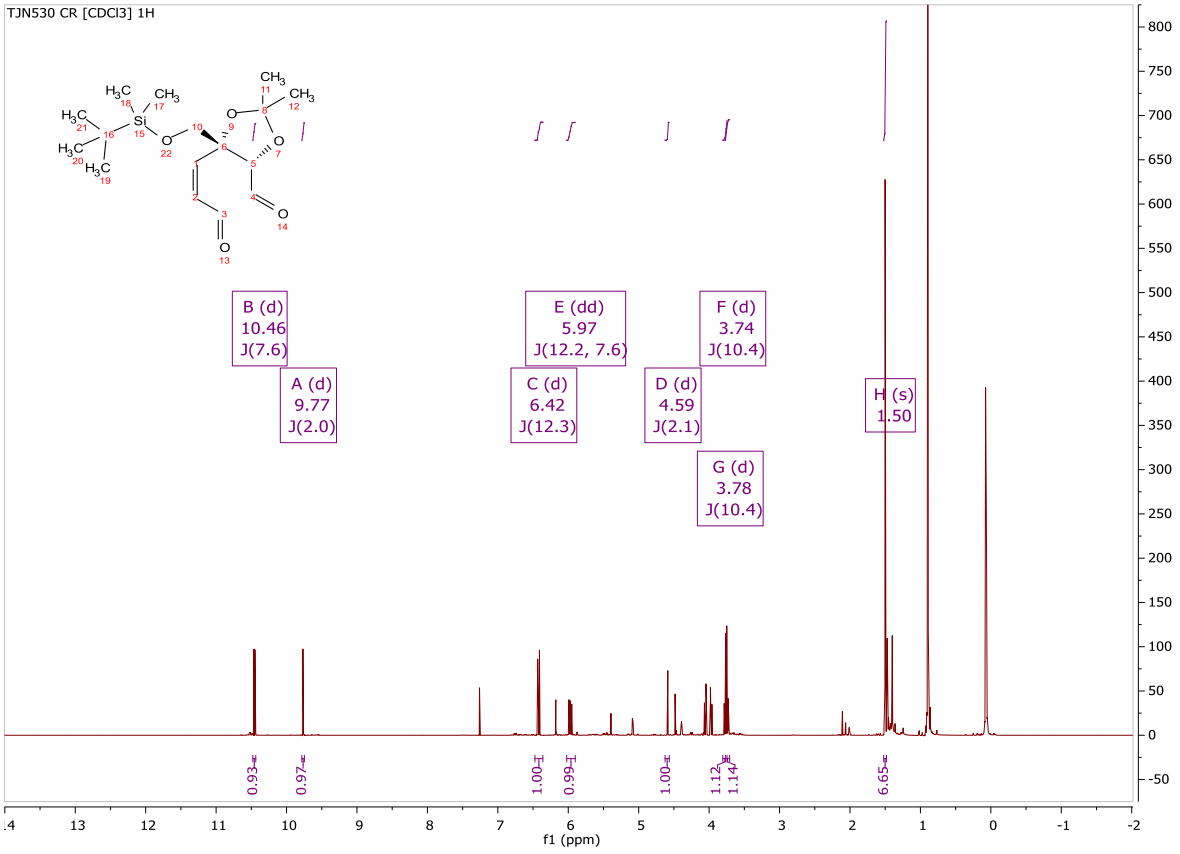
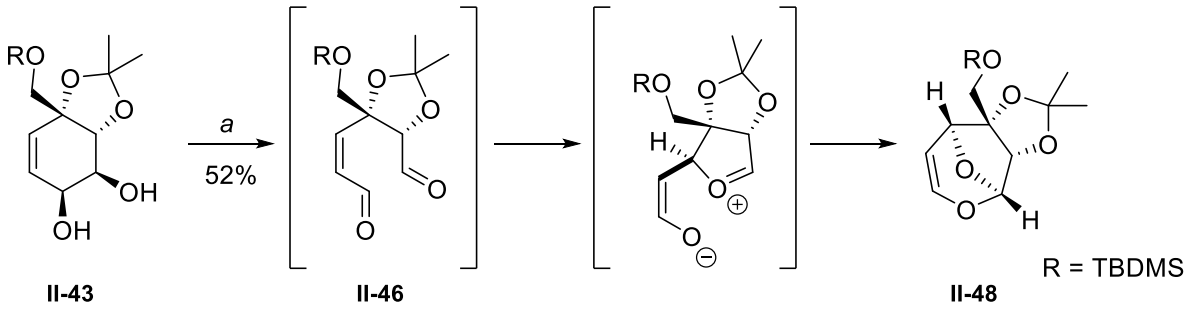


Figure II-05: Crude ^{1}H NMR of dialdehyde **II-46**.

Interestingly, reacting diol **II-43** with $Pb(OAc)_4$ for 16 hours gave a different product – tricyclic **II-48** (scheme II-24). Similarly to the formation of lactol **II-44**, this product too seems to be a result of intramolecular conjugate addition of the aldehyde to the enal. However, in the absence of water, the resulting enolate seemingly attacks the oxonium ion to give **II-48**. This observation suggests that enal

II-46 is highly reactive towards nucleophiles. The stereochemistry of the product has been fully assigned using X-ray crystallography (figure II-06).



II-43 **II-46** **II-48**

Scheme II-24: Synthesis of tricyclic **II-48** with proposed intermediates. *a*) $Pb(OAc)_4$ (1.0 equiv.), MeCN, RT, 16 hours.

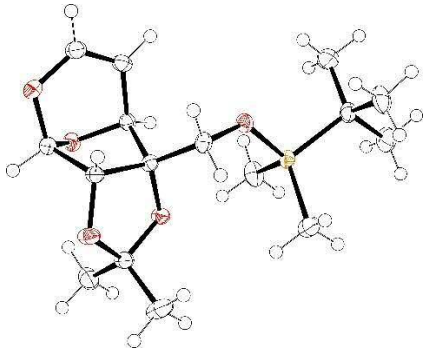
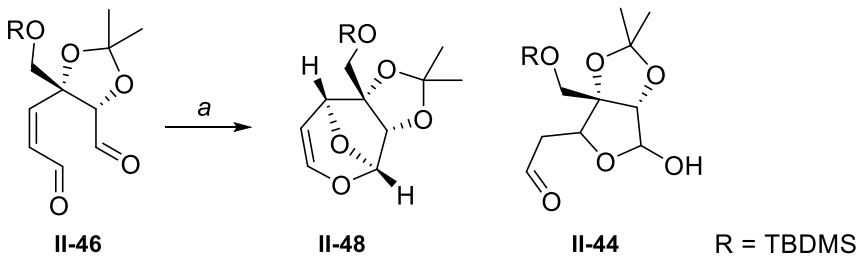


Figure II-06: Crystal structure of poly-cyclic **II-48**.

Reacting crude dialdehyde **II-46** with water in THF did indeed result in the formation of lactol **II-44**, albeit as a minor product when compared to the faster formation of tricyclic **II-48** (scheme II-25). Whilst this set of experiments does help to confirm the series of intermediates produced in the formation of lactol **II-44**, the non-exclusive formation of lactol **II-44** when reacting dialdehyde **II-46** with water in THF does suggest that $NaIO_4$ may play an important role in its formation.

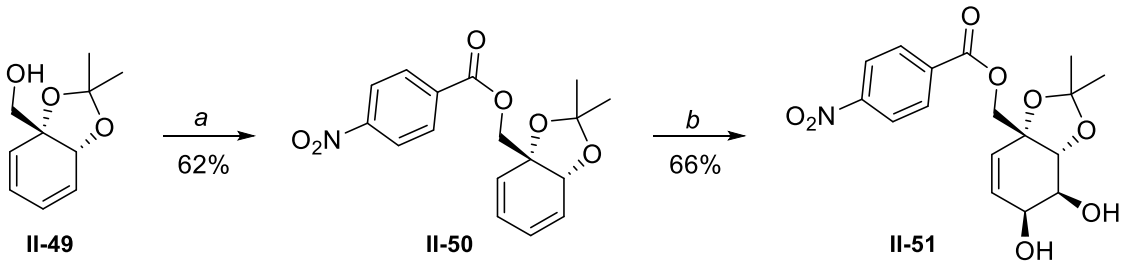


II-46 **II-48** **II-44**

Scheme II-25: Reaction of dialdehyde **II-46** with water in THF. *a*) water, THF, RT, 16 hours.

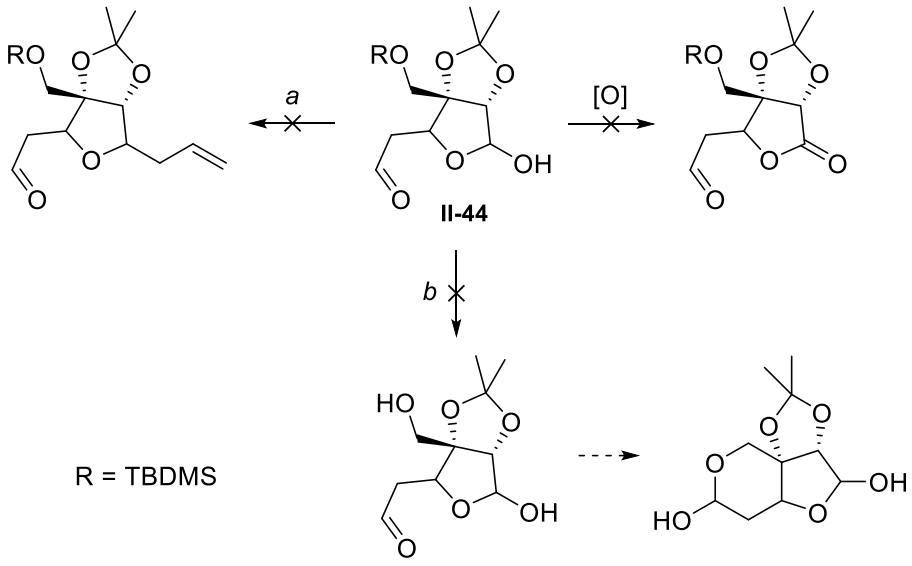
In order to unambiguously assign the stereochemistry of lactol **II-44** and **II-39**, efforts were made to synthesise an analogous lactol which would be crystalline. Doing so would allow an X-ray crystal structure of this compound to be acquired. To this end, alcohol **II-49** was treated with 4-nitrobenzoyl chloride and triethylamine to give ester **II-50** (scheme II-26). Dihydroxylation of this compound

subsequently gave diol **II-51**. Whilst the reaction of diol **II-51** with $NaIO_4$ has been conducted, the purification of the product by recrystallisation, and subsequent growth of crystals suitable for X-ray crystallography, continues to be worked towards.



Scheme II-26: Synthesis of diol **II-51**. *a*) 4-nitrobenzoyl chloride (1.1 equiv.), NEt_3 (1.2 equiv.), CH_2Cl_2, 0°C to RT, 16 hours. *b*) OsO_4 (3 mol%), NMO (1.3 equiv.), acetone, water, RT, 16 hours.

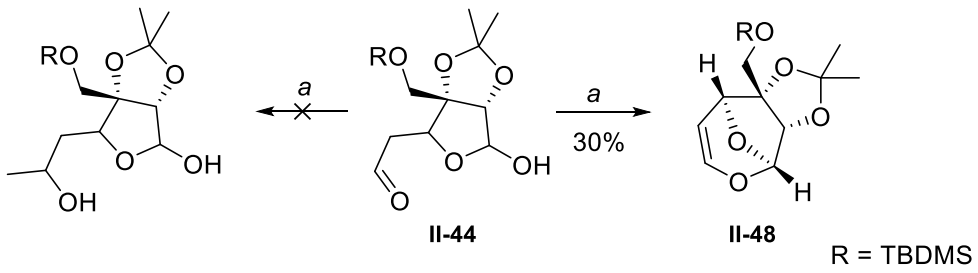
Derivatisation of lactol **II-44** has been pursued, however success has not yet been found in this venture (scheme II-27). Oxidation of the lactol using DMP and SIBX both gave a mixture of a number of compounds, as did Ley oxidation, Swern oxidation and oxidation with PDC. In addition to this, the reaction of lactol **II-44** with $BF_3.Et_2O$ and allyl-TMS also failed to give the desired furan. It was also envisaged that deprotection of the TBDMS group may result in the formation of a second lactol ring, however this too gave a mixture of products.



Scheme II-27: Attempts at derivatising lactol **II-44**. *a*) $BF_3.Et_2O$ (3.1 equiv.), allyl-TMS (2.1 equiv.), CH_2Cl_2, -78°C to RT, 16 hours. *b*) TBAF (1.2 equiv.), THF, -78°C to RT, 16 hours.

Reaction of lactol **II-44** with MeMgBr, however, led once more to the formation of tricyclic **II-48**, and not to methylation of its aldehyde (scheme II-28). This observation suggests that lactol **II-44** may also be reversibly dehydrated, on this occasion using MeMgBr, to form an intermediate which may then participate in the aforementioned intramolecular conjugate addition to afford bicycle **II-48**.

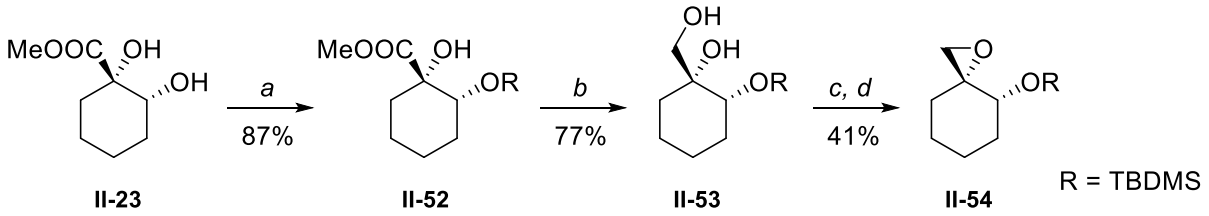
Furthermore, it has also been found that, upon attempted purification of lactol **II-44** by silica gel column chromatography, tricyclic **II-48** also forms.



Scheme II-28: Attempted methylation of lactol **II-44**. *a*) MeMgBr (5.0 equiv.), THF, 0°C to RT, 72 hours.

The diverse and densely packed functionality of lactol **II-44** is desirable for complex, small molecule synthesis, however these features have also presented significant challenges. In particular, the lability of lactol **II-44** has proved a challenge when it comes to derivatising it, necessitating further research to make this strategy of heterocycle synthesis more viable.

The synthesis of spiro-cyclic epoxides from arene diol **II-01** may permit incorporation of various alkyl chains at the tetra-substituted carbon atom through epoxide ring opening reactions. Diol **II-53** was synthesised through TBDMS protection of the secondary alcohol of methyl ester **II-23** to give silyl protected **II-52**, followed by reduction of its methyl ester. Tosylation of the primary alcohol and intra-molecular attack of the tertiary alcohol gave spiro-cyclic epoxide **II-54** (scheme II-29). Whilst this chemistry may be of utility in the future, the synthetic chemistry of epoxide **II-54** has not yet been explored.

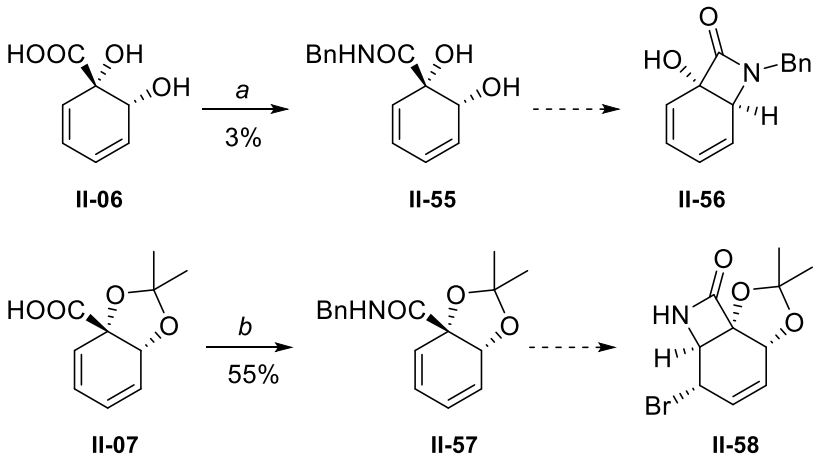


Scheme II-29: Synthesis of spirocyclic epoxide **II-54**. *a*) TBDMSOTf (1.2 equiv.), NEt_3 (2.0 equiv.), CH_2Cl_2, -78°C to RT, 90 minutes. *b*) $LiBH_4$ (2.2 equiv.), THF, -78°C to RT, 16 hours. *c*) *p*TsCl (1.4 equiv.), DMAP (10 mol%), NEt_3 (5.0 equiv.), CH_2Cl_2, 0°C to RT, 20 hours. *d*) K_2CO_3 (1.0 equiv.), MeOH, 0°C to RT, 2 hours.

Benzyne cycloaddition chemistry and reductive aminations

Compounds containing β-lactams are ubiquitous in medicinal chemistry, particularly in antibiotics.[39] As such, the synthesis of novel, enantiopure β-lactams is of interest to expand the pool of compounds that may be useful in medicinal chemistry. The synthesis of β-lactams from arene diol **II-01** was therefore targeted. Two strategies were designed to synthesise β-lactams; the first based on the intramolecular attack of an amide on a tosylated alcohol and the second on the intramolecular attack of an amide on a bromonium ion (similarly to Myers' synthesis of lactones from arene diols).[16]

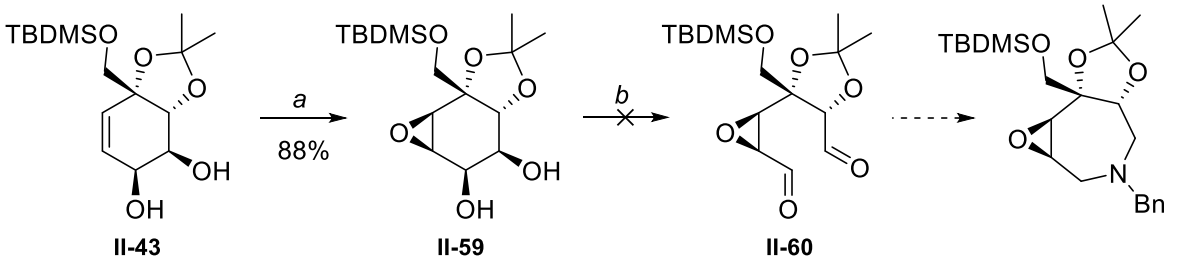
The cyclic propylphosphonic anhydride T3P® is not reported to effect the formation of esters, however it is often used in the synthesis of amides.[40] Since two free alcohols are present on substrate **II-06**, T3P® was consequently identified as a suitable coupling agent for the amidation of **II-06**. Formation of amide **II-55** proved difficult due to base catalysed re-aromatisation of the starting material. Nonetheless, minor amounts of amide **II-55** were synthesised using T3P® (scheme II-30). Other coupling agents have not yet been tested in this transformation, however a reagent screen may be necessary should amide **II-55** be of synthetic utility. In the synthesis of amide **II-57**, the protection of the diol of **II-07** allowed a wider range of suitable coupling agents to be considered. Treating acid **II-07** with benzylamine in the presence of DCC and DMAP gave amide **II-57** in a moderate yield (scheme II-30). Following these early stages of research, Carrera *et al*. published a paper reporting the synthesis of a β-lactam from arene diol **II-01**.[21] Consequentially, the synthesis of amides **II-56** and **II-58** was never attempted and this area of research discontinued.



Scheme II-30: Initial research towards the synthesis of β-lactams. *a*) T3P® (1.1 equiv.), NMM (3.0 equiv.), benzylamine (1.7 equiv.), EtOAc, 0°C to RT, 72 hours. *b*) DCC (1.1 equiv.), DMAP (10 mol%), benzylamine (1.1 equiv.), CH_2Cl_2, RT, 16 hours.

The synthesis of nitrogen containing heterocycles may also be achieved from the reductive amination of dialdehydes, such as dialdeyde **II-60** (scheme II-31). Due to the aforementioned lactol formation reaction when reacting allylic diol **II-43** with $NaIO_4$, it was necessary to first removed the alkene moiety

from this compound prior to dialdehyde formation. To this end, diol **II-43** was epoxidized to give **II-59** (scheme II-31). Reaction of epoxide **II-59** with $NaIO_4$, however, proceeded to give a mixture of compounds. Hydrogenation of alkene **II-43** was also attempted for this sequence of reactions, however hydrogenation was found to proceed extremely slowly under ~1 atmosphere of hydrogen gas. Research by Parker suggests that this reaction may be more successful when conducted under a high pressure of hydrogen gas.[17] Work in this area is ongoing.

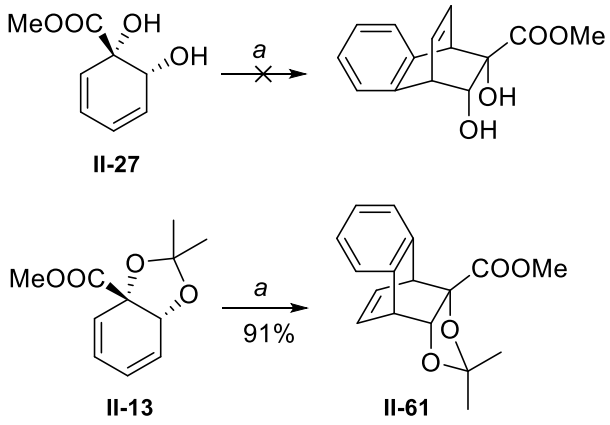


II-43 **II-59** **II-60**

Scheme II-31: Attempted synthesis of dialdehyde **II-60**. *a*) *m*CPBA (2.4 equiv.), CH_2Cl_2, RT, 3 days. *b*) $NaIO_4$ (2.0 equiv.), THF, water, RT, 6 hours.

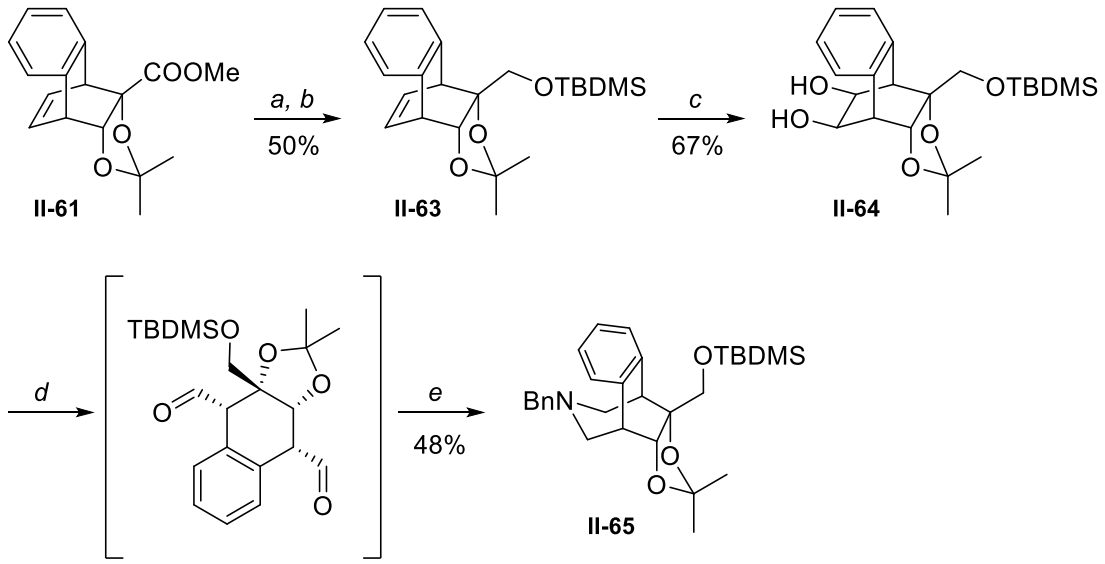
Dienes derived from arene diol **II-01** have been used in several cycloaddition reactions in the past by Widdowson,[41] Mihovilovic[19, 20] and Lewis.[9, 10, 12] However, an emerging trend in synthetic chemistry is to conduct cycloaddition reactions with a source of benzyne, which has been used in the synthesis of benzofurans,[42] benzotriazoles[43] and indazoles.[44] The cycloaddition of benzyne with an *ortho,meta*-arene diol derived diene has previously been reported by Hudlický,[45, 46] however such a cycloaddition has not yet been attempted on dienes derived from *ipso,ortho*-arene diols. Achieving this would give access to 1,2-disubstituted aromatic compounds with fascinating 3D architectures.

Investigation into the reaction of arene *ipso,ortho*-diol derived dienes with benzyne precursors has therefore been undertaken, with Carlos Lopez-Alled (former Masters student at the University of Bath) making a significant contribution to the research. In the reaction of dienes **II-27** and **II-13** with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, benzyne formation was triggered *in situ* through addition of CsF, which affected an elimination reaction with loss of fluorotrimethylsilane and trifluoromethanesulfonate.[47] The reaction of free diol **II-27** with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate failed, resulting in re-aromatised product. However, the cycloaddition between acetonide protected diol **II-13** and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate in the presence of CsF proceeded as planned, giving **II-61** in an excellent yield (scheme II-32). The facial selectivity of this reaction was initially assumed based on the previously reported stereoselectivity of diene **II-13** in cyclo-addition reactions, but was later confirmed by X-ray crystallography of derivative **II-69**.[9, 10, 13, 41]



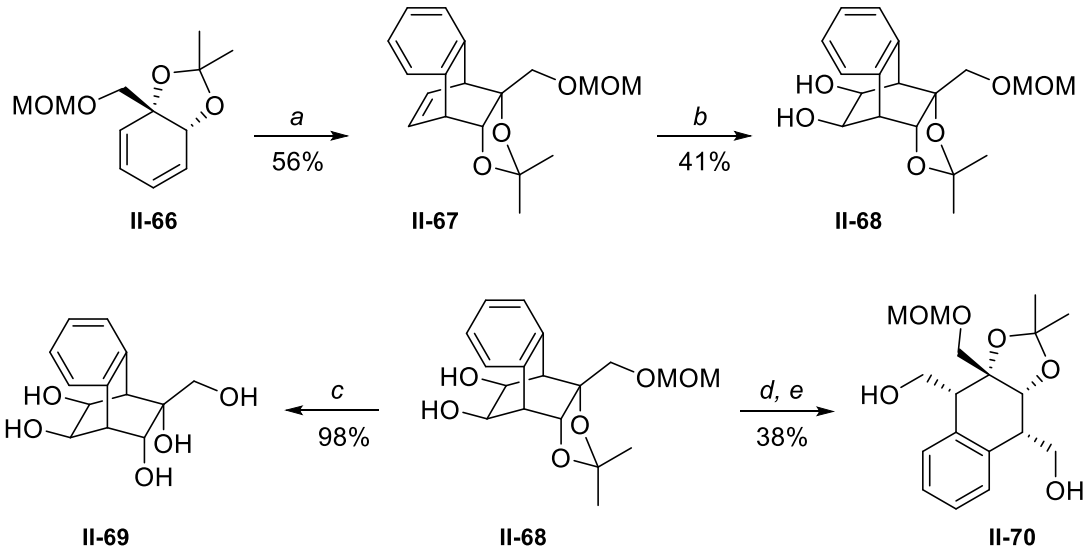
Scheme II-32: Benzyne cycloaddition reaction with diene **II-13**. *a*) 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2.0 equiv.), CsF (4.0 equiv.), MeCN, RT, 16 hours.

Methyl ester **II-61** was subsequently reduced and the resulting alcohol protected as a TBDMS ether to give **II-62** (scheme II-33). OsO_4 mediated dihydroxylation of diene **II-63** gave diol **II-64** in a good yield (scheme II-33). It was envisaged that oxidative cleavage of the glycol bond of **II-64** would give a di-aldehyde, which may then be suitable to conduct a reductive amination on, resulting in a 7-membered *N*-heterocycle. As such, diol **II-64** was reacted with $NaIO_4$ (scheme II-33). The resulting di-aldehyde was not purified or characterised over concerns of epimerisation of the protons α to the aldehydes. Consequentially, it was immediately subjected to reductive amination conditions to furnish *N*-heterocyclic **II-65** in moderate yield (scheme II-33).



Scheme II-33: Synthesis of N-heterocyclic **II-65**. *a*) $LiAlH_4$ (1.8 equiv.), THF, 0°C to RT, 6 hours. *b*) TBDMSOTf (1.2 equiv.), NEt_3 (1.5 equiv.), CH_2Cl_2, -78°C to RT, 24 hours. *c*) OsO_4 (5 mol%), NMO (1.5 equiv.), acetone, water, 45°C, 16 hours. *d*) $NaIO_4$ (2.0 equiv.), THF, water, 3 hours. *e*) Benzylamine (1.05 equiv.), $NaBH(OAc)_3$ (5.0 equiv.), CH_2Cl_2, RT, 16 hours.

In addition to *N*-heterocyclic **II-65**, the synthesis of cyclitols bearing an arene ring has also been achieved. Following synthesis of the MOM protected alcohol **II-66**, reaction with 2-(trimethylsilyl)phenyl trifluoromethanesulfonate and CsF furnished **II-67**, which was subsequently dihydroxylated using catalytic OsO_4 to give diol **II-68** (scheme II-34). Upon acid catalysed global deprotection of diol **II-68**, tri-cyclic cyclitol **II-69** was generated (scheme II-34). An X-ray crystal structure of penta-ol **II-69** was acquired, confirming both the assumed diastereoselectivity of the previous cycloaddition and dihydroxylation reactions (figure II-07). Bicyclic diol **II-70** was also synthesised from diol **II-68** through its reaction with $NaIO_4$ – resulting in cleavage of the glycol bond – followed by immediate reduction of the resulting di-aldehyde (scheme II-34). Whilst global deprotection of diol **II-70** has not yet been attempted, achieving this would give access to another cyclitol bearing an arene ring.



Scheme II-34: Synthesis of penta-ol **II-69** and diol **II-70** from arene diol derived diene **II-66**. *a*) 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (3.0 equiv.), CsF (6.0 equiv.), MeCN, RT, 16 hours. *b*) OsO_4 (5 mol%), NMO (1.0 equiv.), acetone, water, RT, 72 hours. *c*) Acidic ion exchange resin (DOWEX 50W-X8, 20-50 mesh), MeOH, RT, 48 hours. *d*) $NaIO_4$ (24 equiv.), MeOH, water, RT, 6 hours. *e*) $NaBH_4$ (9.8 equiv.), MeOH, 0°C to RT, 24 hours.

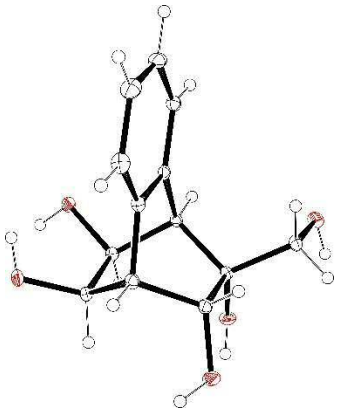
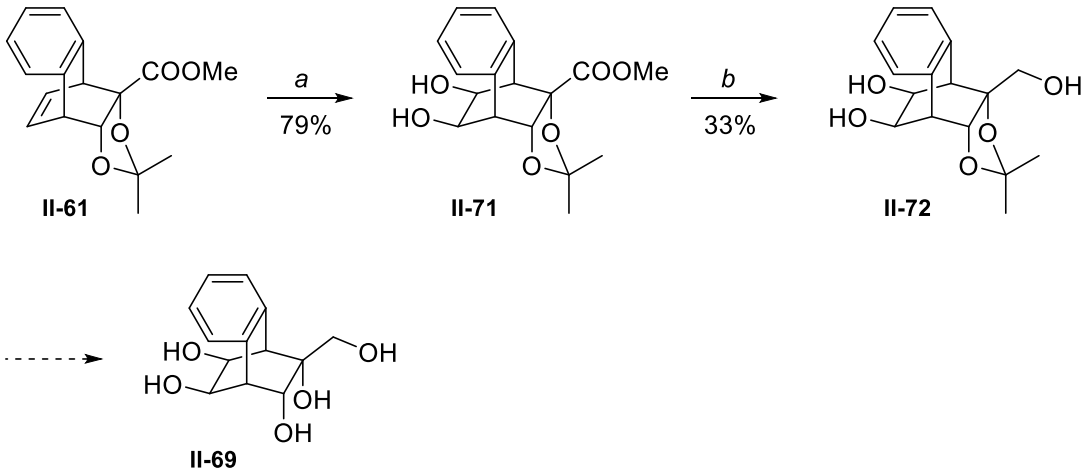


Figure II-07: Crystal structure of cyclitol **II-69**.

In an attempt to reduce the number of synthetic steps required to synthesise cyclitol **II-69**, an alternative synthetic route was devised (scheme II-35). OsO_4 mediated dihydroxylation of alkene **II-61** was conducted to give diol **II-71** in a very good yield. Reduction of the methyl ester to the primary alcohol provided **II-72**. This transformation was achieved in a sub-optimal yield of just 33% yield. The reason for the low yield may be a result of the compound's hydrophilicity; upon aqueous work-up of the reaction, the hydrophilicity of triol **II-72** may have resulted in inefficient extraction from the aqueous phase. Acetonide deprotection of triol **II-72** to form penta-ol **II-72** has not yet been attempted, however developing this chemistry would lead to a more straightforward and atom efficient route to penta-ol **II-72**.

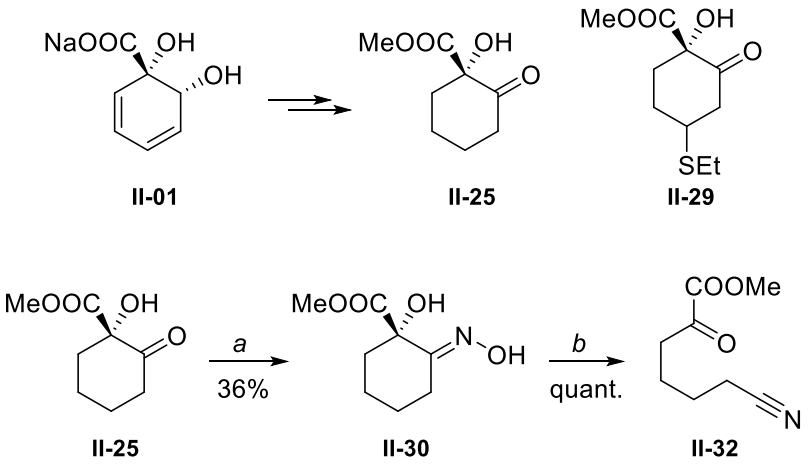


Scheme II-35: Synthesis of triol **II-72**. *a*) OsO_4 (2.5 mol%), NMO (1.5 equiv.), acetone, water, 65°C, 24 hours. *b*) $LiAlH_4$ (2.0 equiv.), THF, 0°C to RT, 4 hours.

Polyhydroxylated compounds have previously been synthesised from arene diols by Parker,[17] Lewis *et al*.,[10, 12] and Myers,[16] and the biology of cyclitols well documentated.[48, 49] The previously detailed work has added to the literature by demonstrating the straightforward synthesis of novel, arene containing cyclitols that possesses a complex 3D structure, as well as novel *N*-heterocyclic **II-65**.

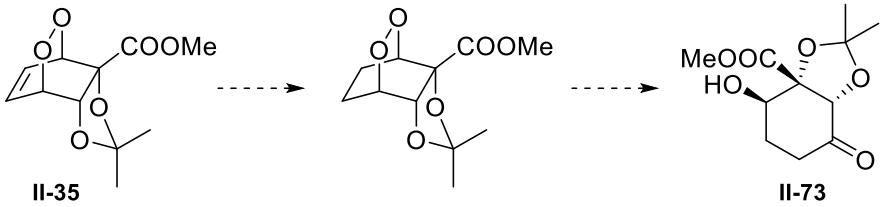
Conclusions and future work

The Beckmann rearrangement allows the synthesis of lactams from ketones.[23, 50] Ketones **II-25** and **II-29** have been synthesised from arene diol **II-01** with the aim of using both in Beckmann rearrangement reactions. However, upon exposing geometrically pure oxime **II-30** to Beckmann rearrangement conditions, Beckmann fragmentation was instead observed to give achiral nitrile **II-32** (scheme II-36). It is postulated that the failure of this reaction was the result of the ketone being situated α to a hydroxyl-bearing tetra-substituted carbon.



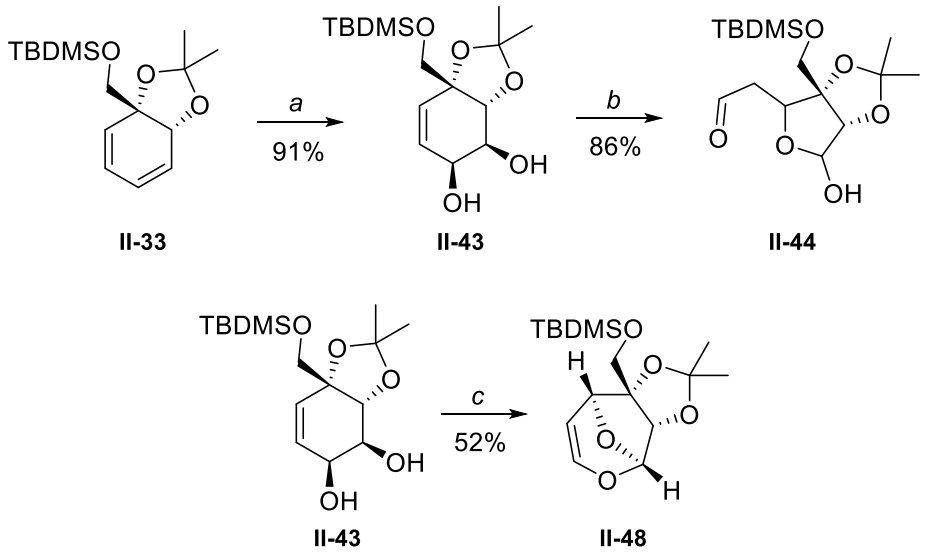
Scheme II-36: Synthesis of ketones **II-25** and **II-29** and the attempted Beckmann rearrangement of oxime **II-30**. *a*) $HONH_2.HCl$ (3.0 equiv.), NaOAc (10 equiv.), MeOH, RT, 16 hours. *b*) thionyl chloride (10 equiv.), THF, 0°C, 3 hours.

Attempts have been made to synthesise ketones from arene diol **II-01** where the ketone moiety was not situated α to a hydroxyl-bearing carbon atom, however difficulties were encountered when trying to achieve this. The synthesis of γ-hydroxy-enone **II-37** from endoperoxide **II-35** was challenging due to the innate reactivity of **II-37**, which resulted in several side reactions occurring. An alternative, and relatively straightforward, method to correct this may be to hydrogenate endo-peroxide **II-35** prior to Kornblum–DeLaMare rearrangement (scheme II-37). This would circumvent the synthesis of a reactive γ-hydroxy-enone Michael acceptor, furnishing instead γ-hydroxy-ketone **II-73**. This product would be a promising substrate upon which to conduct a Beckmann rearrangement reaction.



Scheme II-37: Proposed route to a ketone suitable for Beckmann rearrangement.

Lactol **II-44** has also been synthesised from diene arene diol **II-01** (scheme II-38). This can be achieved in a one-pot reaction from diene **II-33** or through a two-step approach, with diol **II-43** being synthesised prior to glycol cleavage. The two-step strategy furnishes lactol **II-44** with remarkable purity, however despite full characterisation of the product, the stereochemistry of all stereo-centres in the molecule were not possible to assign. It should be made a priority to establish this stereochemistry, which may be achieved through the synthesis of a compound that bears a more crystallisable group in place of the sillyl ether. This would allow an X-ray crystal structure of a similar lactol to **II-44** to be obtained. Tricyclic **II-48** has also been synthesised from diol **II-43** through its reaction with $Pb(OAc)_4$.

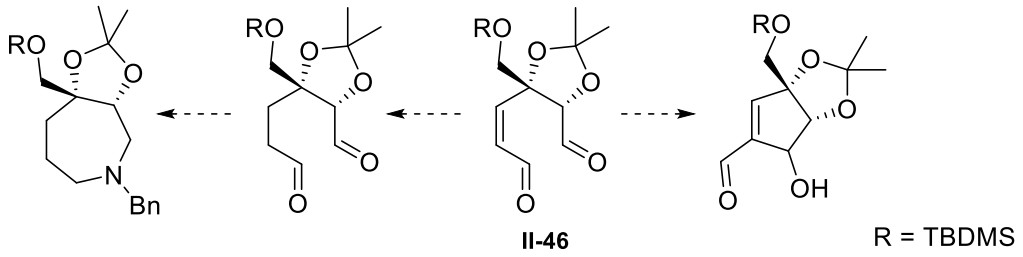


Scheme II-38: Synthesis of lactol **II-44** and tricyclic **II-48** from diene **II-33**. *a*) OsO_4 (2.5 mol%), NMO (1.2 equiv.), acetone, water, 16 hours. *b*) $NaIO_4$ (2 equiv.), THF, water, 8 hours. *c*) $Pb(OAc)_4$ (1.0 equiv.), MeCN, RT, 16 hours.

Derivatisation of lactol **II-44** should continue to be explored. Whilst the synthesis of lactol **II-44** has been shown to be high yielding, reliable and clean, accessing furans or lactones would greatly diversify the number of compounds accessible using this chemistry. Whilst a number of derivatisation protocols have already been attempted, most focus on reactions on the lactol group. It may instead be necessary to protect/derivatise the aldehyde initially, as this may confer greater stability of the product for subsequent reactions.

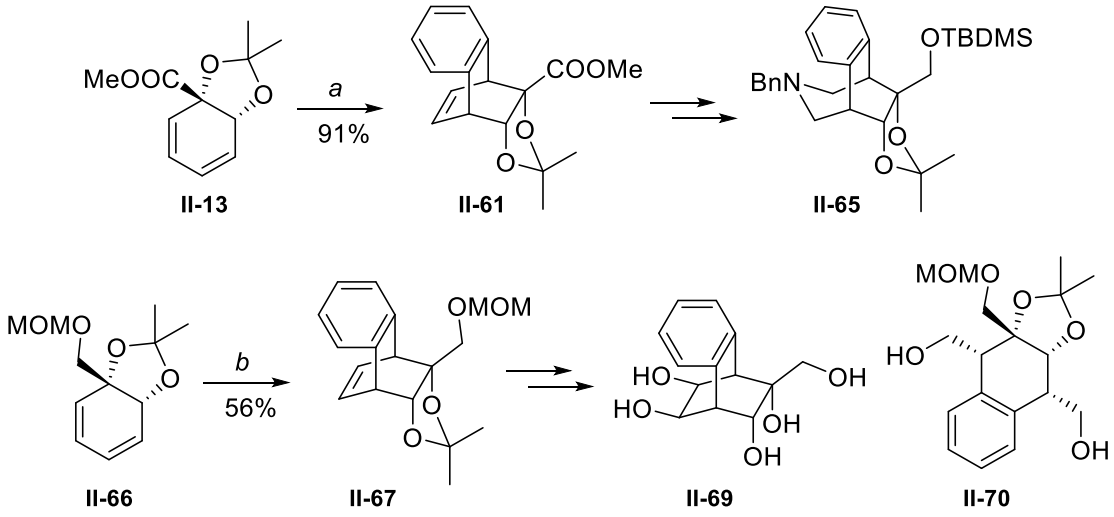
Furthermore, research into dialdehyde **II-46**, which is thought to be an intermediate in the formation of both lactol **II-44** and tricyclic **II-48**, may be of interest. Such dialdehydes have been reported previously in Baylis–Hillman reactions to form cyclopentenes.[38] In addition to this, hydrogenation of or conjugate addition to dialdehyde **II-46** would shut down the lactol and bi-cycle forming pathways and give access to compounds which may be used in reductive amination reactions (scheme II-39).

The reactivity of dialdehyde **II-46** may prove to be of high utility in accessing a wealth of novel, enantiopure compounds from microbially derived arene diols.



Scheme II-39: Proposals for the derivatisation of dialdehyde **II-46**.

Benzyne cyclo-addition chemistry has also been conducted on microbially derived dienes **II-13** and **II-67**. Derivatisation of the resulting arene containing compounds has led to the syntheses of N-heterocyclic **II-65**, cyclitol **II-69** and diol **II-70** (scheme II-40). These compounds are of synthetic interest due to their complex 3D shape and densely packed functionality.

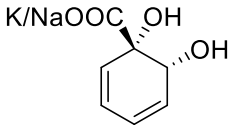


Scheme II-40: Synthesis of *N*-heterocyclic **II-65**, cyclitol **II-69** and diol **II-70** through the use of a benzyne cycloaddition reaction with arene diol derived dienes **II-13** and **II-66**. *a*) 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (2.0 equiv.), CsF (4.0 equiv.), MeCN, RT, 16 hours. *b*) 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (3.0 equiv.), CsF (6.0 equiv.), MeCN, RT, 16 hours.

Despite the synthesis of multiple novel and enantiopure heterocycles from arene diol **II-01**, as well as several other noteworthy compounds synthesised en route, continued research is necessary to fully demonstrate the potential of arene diols in heterocycle synthesis. Research focussed around uses of dialdehyde **II-46** in synthesis and the further development of a Beckmann rearrangement reaction of an arene diol derived oxime are likely to provide further opportunities for success in this area.

Experimental

Potassium/sodium (1*S*,6*R*)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate II-01

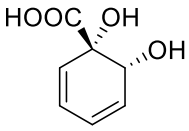


A sterile pipette tip was streaked across a frozen glycerol solution of *Ralstonia eutropha* B9 and added to a sterile solution of Hutner's mineral base (100 mL) and sodium succinate (0.405 g) in an Erlenmeyer flask. The flask was placed on an orbital shaker (250 rpm) at 27°C and shaken for 48 hours. The resulting cloudy suspension was poured into Hutner's mineral base (1.4 L) contained within an Erlenmeyer flask, which was heated to *ca.* 30°C and through which air was bubbled using an airstone. Aqueous D-fructose (10 mL, 10% w/v) was then added, and the culture was left to grow for 24 hours. Following this, the culture was induced with sodium benzoate (1.0 M, 8.0 mL) and fed a further quantity of D-fructose (8.0 mL). After 16 h, repetitive feeding of sodium benzoate and D-fructose began, with a total of 200 mL of sodium benzoate and 200 mL of D-fructose being added to the culture over a period of 5 days (40 mL/ 24 h). A final quantity of D-fructose (20 mL) was then added over the next 24 hours in order to ensure full conversion of all the added substrate.

The culture was centrifuged (5000 rpm, 45 minutes, 4°C) and the supernatant collected. The volume of the supernatant was reduced to ~150 mL through concentration under vacuum. Isopropanol (850 mL) was added, which effected precipitation of a brown solid. The solid was then filtered off, re-dissolved in water (80 mL) and isopropanol (800 mL) added; this was found to aid in the removal of residual media salts and excess D-fructose. The product was again isolated by filtration, washed with CH_2Cl_2 and dried under vacuum to give a cream coloured solid (16.4 g), which contained **II-01** as the mixed sodium/potassium carboxylate salt and a variable proportion of growth medium salts.

^{1}H NMR (500 MHz, DMSO) δ = 5.79 (1H, dd, J = 9.5, 5.2 Hz), 5.75-5.67 (1H, m), 5.61-5.54 (1H, m), 5.51 (1H, d, J = 9.5 Hz), 4.68-4.63 (1H, m). Data are in agreement with those previously reported.[20]

(1*S*,6*R*)-1,6-Dihydroxycyclohexa-2,4-diene-1-carboxylic acid II-06

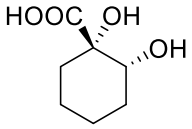


Carboxylate **II-01** (16.4 g, 92.1 mmol (assuming solid contains no residual media salts)) was dissolved in water (1.0 L). The solution was cooled to ~0°C and carefully acidified to between pH 2.5 and 3.0 with aq. conc. HCl. Carboxylic acid **II-06** was extracted with EtOAc (10 x 2 L), ensuring the pH of the aqueous phase remained between pH 2.5 and 3.0 and each extraction. The solvent was removed

under vacuum (water bath 30°C), and the product triturated with CH_2Cl_2 (2 x 50 mL) to give pure acid diol **II-06** as an off-white solid (8.00 g, 51.3 mmol, 56%).

^{1}H NMR (500 MHz, CD_3OD) δ = 6.10 (1H, dd, J = 9.7, 5.2 Hz), 5.93 (1H, dddd, J = 9.2, 5.2, 2.8, 1.2 Hz), 5.83-5.76 (2H, m), 4.87-4.82 (1H, m); ^{13}C NMR (126 MHz, CD_3OD) δ = 178.0, 133.6, 127.3, 127.1, 123.5, 75.4, 72.4. Data are in agreement with those previously reported.[12]

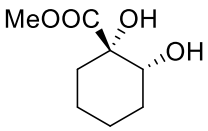
(1*S*,2*R*)-1,2-Dihydroxycyclohexane-1-carboxylic acid II-22



To acid diol **II-06** (5.48 g, 35.1 mmol) and Pd/C (0.700 g) was added MeOH (80 mL). The suspension was stirred under an atmosphere of H_2 gas (balloon) for 23 hours, and the suspension then filtered through Celite. The solvent was removed under vacuum, and the product triturated with cold CH_2Cl_2 (2 x 30 mL) to remove unwanted re-aromatisation products. **II-22** was obtained as an off-white solid (3.49 g, 21.8 mmol, 62%) and was found to be of good purity, meaning that no purification was necessary.

^{1}H NMR (500 MHz, CD_3OD) δ = 3.83 (1H, dd, J = 11.5, 4.5 Hz), 1.81-1.27 (8H, m); ^{13}C NMR (126 MHz, CD_3OD) δ = 179.1, 77.9, 73.6, 35.3, 30.8, 25.4, 21.1. Data are in agreement with those previously reported.[12]

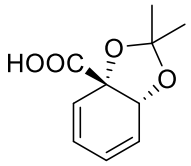
Methyl (1*S*,2*R*)-1,2-dihydroxycyclohexane-1-carboxylate II-23



To a solution of saturated diol acid **II-22** (1.28 g, 8.08 mmol) in MeOH (40 mL) and benzene (40 mL) was added TMS-CHN_2 (~ 12.5 mL, "2M" in hexanes), until a luminous yellow colour persisted in solution. The solution was left to stir for 20 minutes, and the solvent was removed under vacuum. The crude product was purified by column chromatography (30% EtOAc, 70% petroleum ether) to give **II-23** as a white solid (0.975 g, 5.60 mmol, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.87-3.76 (1H, m), 3.81 (3H, s), 3.31 (1H, m, O**H**), 2.02 (1H, s, O**H**), 1.91-1.21 (8H, m). HRMS (ESI+) *m/z* calculated for $(C_8H_{14}O_4Na)$+ 197.0784; found 197.0861. Data are in agreement with those previously reported.[12]

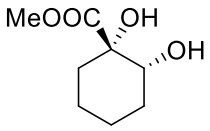
(3a*S*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylic acid II-07



A suspension of diol carboxylate **II-01** (1.90 g, 9.69 mmol, 1.0 equiv.) in 2,2-DMP (70 mL) was cooled to 0°C and TFA (3.7 mL, 48.4 mmol, 5.0 equiv.) added dropwise over 10 minutes. The suspension was allowed to warm to RT over 24 h and then filtered through a pad of Celite. The solution was concentrated under vacuum and then resuspended in water (50 mL). The product was extracted with CH_2Cl_2 (2 x 50 mL). Organic extracts were combined, dried over $MgSO_4$ and the solvent removed to give **II-07** as a brown oil (1.69 g, 8.62 mmol, 89%). This brown oil was of acceptable purity to use in subsequent synthetic steps.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.19-6.12 (2H, m), 6.04-6.00 (1H, m), 5.81-5.78 (1H, m), 4.95 (1H, dd, J = 4.1, 0.9 Hz), 1.49 (3H, s), 1.43 (3H, s). HRMS (ESI-) *m/z* calculated for $(C_{10}H_{11}O_4)$- 195.0663; found 195.0674. Data are in agreement with those previously reported.[21]

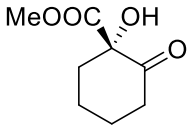
Methyl (1*S*,2*R*)-1,2-dihydroxycyclohexane-1-carboxylate II-23



Through a suspension of acid diene **II-07** (0.558 g, 0.285 mmol, 1.0 equiv.) and Pd/C (60 mg) in EtOAc (20 mL) was bubbled H_2 gas for 16 hours. The suspension was filtered through a pad of Celite and the solvent removed to give a brown oil. This oil was immediately re-dissolved in MeOH (30 mL) and *p*TSA added (56 mg, 0.292 mmol, 1.0 equiv.) and the solution stirred for 5 days. NaOAc (100 mg) was added and the suspension filtered. The solvent was removed under vacuum to give a brown oil, which was purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **II-23** as a white solid (0.307 g, 0.176 mmol, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.87-3.76 (1H, m), 3.81 (3H, s), 3.31 (1H, m, O**H**), 2.02 (1H, s, O**H**), 1.91-1.21 (8H, m). HRMS (ESI+) *m/z* calculated for $(C_8H_{14}O_4Na)$+ 197.0784; found 197.0861. Data are in agreement with those previously reported.[12]

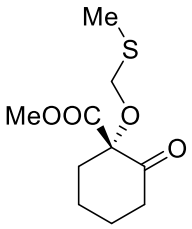
Methyl (*S*)-1-hydroxy-2-oxocyclohexane-1-carboxylate II-25



A suspension of SIBX (45% wt IBX, 3.91 g, 6.28 mmol, 2.0 equiv.) and DMSO (10 mL) was stirred until full dissolution of SIBX (~10 minutes). Alcohol **II-23** (0.547 g, 3.14 mmol, 1.0 equiv.) in DMSO (5.0 mL) was then added slowly. After addition of **II-23**, the solution was heated to 60°C and stirred for 3 h. The solution was then allowed to cool to RT, and TFA (0.48 mL, 6.28 mmol, 2.0 equiv.) added. Stirring was continued for a further 2 h. EtOAc (20 mL) was added to the solution, and the organic layer was washed with saturated, aqueous $NaHCO_3$ (2 x 15 mL), aqueous sodium thiosulfate (10%, 2 x 15 mL) and brine (2 x 15 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum to give **II-25** as a yellow oil (0.370 g, 2.15 mmol, 68%) of good purity.

Rf = 0.35 (30% EtOAc, 70% petroleum ether); $[\alpha]_D^{26}$ = -99 (CH_2Cl_2, *c*. 0.73 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.79 (3H, s), 2.78-2.53 (3H, m), 2.11-2.00 (1H, m), 1.98-1.62 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 207.4, 170.7, 80.9, 53.1, 39.0, 38.0, 27.2, 22.1; ν_{max} (film) 3458, 2953, 2868, 1716, 1438, 1249, 1214, 1114, 1093 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_8H_{12}O_4Na)$+ 195.0628; found 195.0610.

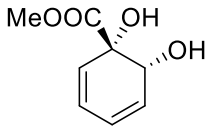
Methyl (*S*)-1-((methylthio)methoxy)-2-oxocyclohexane-1-carboxylate II-26



DMSO (90 µL, 1.16 mmol, 2.0 equiv.) in CH_2Cl_2 (10 mL) was cooled to -78°C and oxalyl chloride (73 µL, 0.578 mmol, 1.0 equiv.) was added dropwise. Stirring at -78°C continued for 15 minutes, at which point diol **II-23** (0.100 g, 0.578 mmol, 1.0 equiv.) was added dropwise and the reaction stirred for a further 15 minutes. Triethylamine (0.400 mL, 2.89 mmol, 5.0 equiv.) was added dropwise, and stirring continued for a final 30 minutes. The solution was then warmed to 0°C, stirred for 15 minutes and poured into CH_2Cl_2 (25 mL). The resulting solution was washed with water (20 mL), saturated aqueous NH_4Cl (20 mL), water (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum to give an oil. The oil was purified by column chromatography (10% EtOAc, 90% Petroleum ether) to give **II-26** as a colourless oil (23 mg, 0.099 mmol, 17%).

R_f = 0.53 (25% EtOAc, 75% petroleum ether); $[\alpha]_D^{26}$ = -3.5 (CH_2Cl_2, *c*. 1.25 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.80 (1H, d, J = 10.9 Hz), 4.67 (1H, d, J = 10.9 Hz), 3.80 (3H, s), 2.76-2.66 (1H, m), 2.52-2.42 (1H, m), 2.41-2.32 (1H, m), 2.26 (3H, s), 2.09 (1H, dddd, J = 14.2, 7.3, 3.6, 1.9 Hz), 1.96-1.79 (3H, m), 1.72-1.61 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 205.8, 170.2, 86.4, 71.1, 52.7, 40.2, 36.0, 27.1, 21.0, 14.8; ν_{max} (film) 2950, 2867, 1746, 1721, 1435, 1247, 1097, 1032, 998 cm-1; HRMS (ESI+) *m/z* calculated for $(C_{10}H_{15}O_4SNa)$+ 255.0662; found 255.0676.

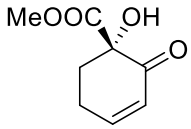
Methyl (1*S*,6*R*)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate II-27



To a solution of diol acid **II-06** (0.546 g, 3.50 mmol) in MeOH (10 mL) and benzene (10 mL) was added TMS-diazomethane (~3.5 mL, "2M" in hexanes) slowly until a yellow colour persisted in solution and effervescence ceased. The yellow solution was stirred for 20 minutes before the solvent was removed under vacuum and the crude product purified by column chromatography (30% EtOAc, 70% petroleum ether → 50% EtOAc, 50% petroleum ether) to give methyl ester **II-27** as a white solid (0.492 g, 2.89 mmol, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.11 (1H, ddt, J = 9.5, 5.3, 0.8 Hz), 5.92 (1H, dddd, J = 9.8, 5.4, 2.8, 1.1 Hz), 5.79 (1H, ddt, J = 9.7, 2.3, 1.0 Hz), 5.74 (1H, dq, J = 9.6, 1.1 Hz), 4.81 (1H, dt, J = 9.0, 2.9 Hz), 3.84 (3H, s), 3.71 (1H, s, O**H**), 3.00 (1H, d, J = 10.2 Hz). HRMS (ESI+) *m/z* calculated for $(C_8H_{10}O_4Na)$+ 193.0471; found 195.0499. Data are in agreement with those previously reported.[14]

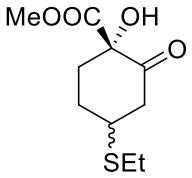
Methyl (*S*)-1-hydroxy-2-oxocyclohex-3-ene-1-carboxylate II-28



Diene **II-27** (0.692 g, 4.07 mmol, 1.0 equiv.), Grubbs' 1st generation catalyst (0.165 g, 0.200 mmol, 5 mol%) and toluene (15 mL) were heated to reflux and stirred for 18 hours. The solvent was removed under reduced pressure to give a black oil. This was then purified by flash column chromatography (25% EtOAc, 75% petroleum ether) to give **II-28** as a light brown oil (70 mg, 0.412 mmol, 10%).

^{1}H NMR (250 MHz, CDCl3) δ = 7.09-6.98 (1H, m), 6.10 (1H, d, J = 10.1 Hz), 4.29 (1H, s, O**H**), 3.73 (3H, s), 2.71-2.42 (3H, m), 2.30-2.04 (1H, m). Data are in agreement with those previously reported.[14]

Methyl (1*S*)-4-(ethylthio)-1-hydroxy-2-oxocyclohexane-1-carboxylate II-29



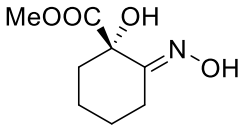
To enone **II-28** (52.0 mg, 0.301 mmol, 1.0 equiv.) and ethanethiol (24.0 µL, 0.331 mmol, 1.1 equiv.) in $CHCl_3$ (3.0 mL) was added trimethylamine (0.50 mL). The solution was heated to 30°C and stirred for 22 hours. After this time, Et_2O (10 mL) was added and the solution washed with aqueous HCl (3 wt%, 3 x 10 mL) and water (10 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum to give an orange oil. This oil was purified by flash column chromatography (20% EtOAc, 80% petroleum ether) to give an orange, waxy oil (0.032 g, 0.136 mmol, 45%). The product was determined to be a mixture of 2 diastereomers in a ratio of 64:34, which were characterised from analysis of the crude mixture.

R_f = 0.48 (25% EtOAc, 75% petroleum ether); ν_{max} (film) 3444, 2956, 2930, 2878, 1718, 1437, 1253, 1170, 1110, 1075, 979 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{10}H_{16}O_4SNa)+$ 255.0662, found 255.0664.

NMR data for major product: ^1H NMR (500 MHz, $CDCl_3$) δ = 3.80 (3H, s), 3.36 (1H, apparent p, J = 5.7 Hz), 2.92 (1H, dd, J = 14.2, 4.9 Hz), 2.82 (1H, dd, J = 14.3, 6.3 Hz), 2.62-2.49 (2H, m), 2.42 (1H, ddd, J = 13.7, 6.9, 3.5 Hz), 2.26-2.11 (2H, m), 2.04-1.95 (1H, m), 1.30-1.20 (3H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 204.5, 171.2, 80.1, 53.3, 44.1, 42.3, 33.6, 27.2, 24.8, 14.7.

NMR data for minor product: ^1H NMR (500 MHz, $CDCl_3$) δ = 3.79 (3H, s), 3.04-2.94 (2H, m), 2.73 (1H, dt, J = 13.9, 4.1 Hz), 2.66 (1H, dd, J = 14.1, 12.2 Hz), 2.62-2.49 (2H, m), 2.26-2.11 (1H, m), 1.90 (1H, dddd, J = 14.9, 13.1, 11.2, 3.8 Hz), 1.65 (1H, td, J = 13.3, 4.1 Hz), 1.30-1.20 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 204.5, 170.1, 80.2, 53.3, 45.5, 42.6, 35.8, 29.3, 24.8, 14.9.

Methyl *E*-(S)-1-hydroxy-2-(hydroxyimino)cyclohexane-1-carboxylate II-30

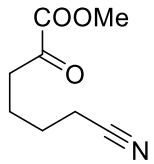


To ketone **II-25** (0.130 g, 0.756 mmol, 1.0 equiv.), hydroxylamine hydrochloride (0.158 g, 2.27 mmol, 3.0 equiv.) and NaOAc (1.04 g, 7.56 mmol, 10 equiv.) was added MeOH (5.0 mL). The suspension was stirred for 16 hours at RT. The solvent was then removed under vacuum and the resulting solid re-dissolved in water (20 mL). The product was extracted with EtOAc (3 x 20 mL). Organic extracts were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The resulting solid was purified by recrystallisation with EtOAc and petroleum ether to give **II-30** as a white solid (51 mg, 0.273 mmol, 36%).

R_f = 0.42 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = +47 (CH_2Cl_2, *c*. 0.77 g/100 mL); melting point = 103-106°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.80 (3H, s), 2.89 (1H, dt, J = 14.8, 4.9 Hz), 2.43 (1H, ddd, J = 15.5, 10.8, 5.2 Hz), 2.19 (1H, ddd, J = 13.6, 10.7, 4.1 Hz), 1.93-1.62 (4H, m), 1.60-1.48 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 174.0, 160.0, 76.2, 53.1, 36.0, 24.6, 21.6, 20.8; ν_{max} (film) 3353, 2974, 2952, 2925, 2867, 1717, 1442, 1281, 1160, 1017, 937 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_8H_{13}O_4NH)$+ 188.0917, found 188.0927.

Crystal structure data for **II-30** to be found in the appendix.

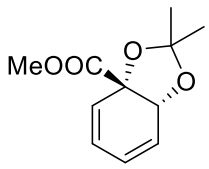
Methyl 6-cyano-2-oxohexanoate II-32



A solution of $SOCl_2$ (0.8 mL, 1.10 mmol, 10 equiv.) in anhydrous THF (1.5 mL) was cooled to 0°C. Oxime **II-30** (20 mg, 0.107 mmol, 1.0 equiv.) in THF (0.5 mL) was added dropwise and the solution was stirred at 0°C for 3 hours. After this time, the reaction was quenched through addition of water (10 mL) and extracted with EtOAc (3 x 10 mL). Organic layers were combined, washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum to give **II-32** as a yellow oil (19 mg, 1.10 mmol, quantitative) which was characterised by NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.87 (3H, s), 2.91 (2H, t, J = 6.9 Hz), 2.38 (2H, t, J = 7.0 Hz), 1.87-1.66 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 193.2, 161.3, 119.3, 53.2, 38.4, 24.7, 22.1, 17.2.

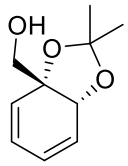
Methyl (3a*S*,7a*R*)-2,2-dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylate II-13



Acid diene **II-07** (1.20 g, 6.10 mmol) was dissolved in MeOH (20 mL) and benzene (20 mL) and TMS-diazomethane (~6 mL, "2M" in hexanes) added slowly until a yellow colour persisted in solution and effervescence ceased. The solution was stirred for 20 minutes, the solvent removed under vacuum and the product purified by column chromatography (15% EtOAc, 85% petroleum ether) to give **II-13** as a colourless oil (0.843 g, 4.01 mmol, 66%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.11-6.02 (2H, m), 6.02-5.93 (1H, m), 5.82-5.74 (1H, m), 4.93 (1H, dd, J = 4.2, 0.7 Hz), 3.75 (3H, s), 1.40 (3H, s), 1.38 (3H, s); HRMS (ESI+) *m/z* calculated $(C_{11}H_{14}O_4Na)^+$ 233.0784, found 255.0784. Data are in agreement with those previously reported.[22]

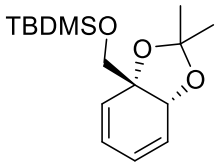
((3a*R*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methanol II-49



Methyl ester **II-13** (1.41 g, 6.71 mmol, 1.0 equiv.) was dissolved in anhydrous THF (15 mL) and cooled to 0°C. $LiBH_4$ (4.0 M, 3.4 mL, 13.4 mmol, 2.0 equiv.) was added dropwise and the solution allowed to warm to RT over 16 h. The reaction was quenched through addition of EtOAc (20 mL) followed by water (20 mL). The organic phase was collected and the product further extracted from the aqueous phase using EtOAc (2 x 20 mL). Organic phases were combined and dried over $MgSO_4$. The solvent was removed under vacuum to give **II-49** a colourless oil (1.03 g, 0.566 mmol, 84%). The product obtained was of good purity, so no further purification was necessary.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.06 (1H, dd, J = 9.7, 5.2 Hz), 6.02-5.95 (2H, m), 5.67 (1H, d, J = 9.9 Hz), 4.46 (1H, d, J = 4.7 Hz), 3.56 (1H, dd, J = 12.0, 2.9 Hz), 3.34 (1H, dd, J = 11.9, 7.1 Hz), 2.22-2.15 (1H, m), 1.42 (3H, s), 1.34 (3H, s); HRMS (ESI+) *m/z* calculated $(C_{10}H_{14}O_3Na)^+$ 205.0835, found 205.0841. Data are in agreement with those previously reported.[10]

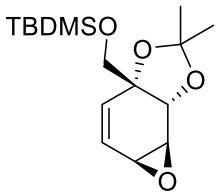
***tert*-Butyl(((3a*R*,7a*R*)-2,2-dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methoxy)dimethylsilane II-33**



Alcohol **II-49** (0.285 g, 1.57 mmol, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (8.0 mL) and cooled to -78°C. Triethylamine (0.26 mL, 1.88 mmol, 1.2 equiv.) was added dropwise, followed by TBDMSOTf (0.38 mL, 1.64 mmol, 1.05 equiv.) and the solution allowed to warm to RT over 16 hours. Water (20 mL) was then added and the product extracted with CH_2Cl_2 (2 x 20 mL). Organic phases were combined and dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (5% EtOAc, 95% petroleum ether) to give **II-33** as a colourless oil (0.395 g, 1.33 mmol, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.07 (1H, ddt, J = 9.6, 5.3, 0.6 Hz), 6.00 (1H, tt, J = 5.0, 1.0 Hz), 5.97 (1H, ddd, J = 9.7, 5.3, 1.1 Hz), 5.67 (1H, dq, J = 9.7, 0.8 Hz), 4.52 (1H, d, J = 4.6 Hz), 3.61 (1H, d, J = 10.5 Hz), 3.44 (1H, d, J = 10.5 Hz), 1.43 (3H, s), 1.36 (3H, s), 0.88 (9H, s), 0.05 (3H, s), 0.04 (3H, s). Data are in agreement with those previously reported.[10]

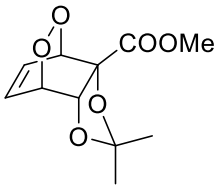
tert-Butyl(((3a*R*,5a*S*,6a*S*,6b*R*)-2,2-dimethyl-6a,6b-dihydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxol-3a(5aH)-yl)methoxy)dimethylsilane II-34



Diene **II-33** (0.184 g, 0.621 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to 0°C. *m*CPBA (0.139 g, 0.808 mmol, 1.3 equiv.) was added and the solution allowed to warm to RT over 14 hours. Following this, a further quantity of *m*CPBA (10 mg, 57.9 µmol, 0.1 equiv.) was added and the solution stirred for a further 5 hours. The reaction was quenched through the addition of aqueous sodium thiosulfate (1.0 M, 20 mL) and the product extracted with CH_2Cl_2 (3 x 20 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (5% EtOAc, 95% petroleum ether) to give **II-34** as a colourless oil (0.145 g, 0.464 mmol, 75%).

Rf = 0.25 (5% EtOAc, 95% petroleum ether); $[\alpha]_D^{25}$ = -31 (CH_2Cl_2, *c*. 1 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.03 (1H, dd, J = 10.2, 4.0 Hz), 5.66 (1H, dt, J = 10.2, 1.3 Hz), 4.73 (1H, dt, J = 2.0, 0.9 Hz), 3.68 (1H, d, J = 10.9 Hz), 3.63 (1H, dd, J = 3.7, 2.2 Hz), 3.43 (1H, d, J = 10.9 Hz), 3.37-3.34 (1H, m), 1.42 (3H, s), 1.37 (3H, s), 0.91 (9H, s), 0.07 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 134.2, 123.4, 110.0, 81.5, 69.9, 66.4, 50.9, 46.9, 28.2, 27.0, 26.1, 18.6, -5.1, -5.3; ν_{max} (film) 2989, 2955, 2930, 2858, 1463, 1368, 1253, 1217, 1083, 1053, 829 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{28}O_4SiNa)^+$ 335.1649, found 335.1654.

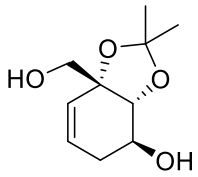
Methyl (3a*R*,4*R*,7*S*,7a*R*)-2,2-dimethyl-7,7a-dihydro-4,7-epidioxybenzo[d][1,3]dioxole-3a(4H)-carboxylate II-35



Diene **II-13** (0.232 g, 1.10 mmol) was dissolved in CH_2Cl_2 (5.0 mL) and TPP (0.1 mL, 30 mg/mL solution) added. The solution was cooled to ~0°C. Four needles attached to an oxygen cylinder delivered oxygen to the solution for 8 h, whilst the solution was irradiated by five L.E.D. lights (12 V). The solvent was removed and analysis of the crude ^{1}H NMR showed 90% conversion of the starting material. The crude product was purified by column chromatography (20% EtOAc, 80% petroleum ether) to give **II-35** as an off-white solid (0.152 g, 0.628 mmol, 57%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.59-6.55 (2H, m), 5.14 (1H, d, J = 4.9 Hz), 5.11-5.08 (1H, m), 4.97-4.93 (1H, m), 3.85 (3H, s), 1.30 (3H, s), 1.28 (3H, s); HRMS (ESI+) *m/z* calculated $(C_{11}H_{14}O_6Na)^+$ 265.0683, found 223.0704. Data are in agreement with those previously reported.[10]

(3a*R*,4*S*,7a*R*)-7a-(Hydroxymethyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol II-36

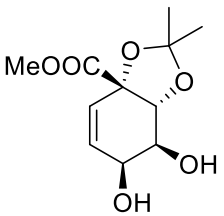


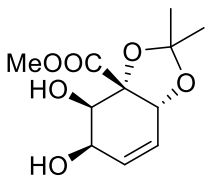
Epoxide **II-34** (91 mg, 0.291 mmol, 1.0 equiv.) was dissolved in anhydrous THF (5.0 mL) and cooled to 0°C. $LiAlH_4$ (2.4 M in THF, 0.24 mL, 0.582 mmol, 2.0 equiv.) was added dropwise and the reaction allowed to warm to RT over 16 hours. The reaction was cooled to 0°C and quenched through slow addition of water (10 mL). The resulting suspension was filtered and the product extracted with EtOAc (2 x 10 mL). The solvent was removed under vacuum and the crude product purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **II-36** as a white solid (32 mg, 0.160 mmol, 55%).

R_f = 0.25 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = -34 (CH_2Cl_2, *c*. 1 g/100 mL); melting point = 103-105°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.81 (1H, dddd, J = 10.3, 5.2, 2.4, 1.1 Hz), 5.52 (1H, ddt, J = 10.3, 2.8, 1.3 Hz), 4.25-4.21 (1H, m), 4.12 (1H, d, J = 4.0 Hz), 3.66 (1H, d, J = 10.8 Hz), 3.59 (1H, d, J = 10.9 Hz), 3.48 (2H, s, O**H**), 2.46 (1H, ddt, J = 18.1, 4.2 2.7 Hz), 2.17-2.10 (1H, m), 1.38 (3H, s), 1.36 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 127.4, 127.2, 108.9, 79.4, 78.4, 66.2, 66.0, 28.8, 28.0, 27.5; ν_{max} (film) 3325, 2985, 2931, 1371, 1236, 1221, 1052, 903 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{10}H_{16}O_4Na)^+$ 223.0941, found 223.0943.

Methyl (3a*S*,6*S*,7*S*,7a*R*)-6,7-dihydroxy-2,2-dimethyl-7,7a-dihydrobenzo[d][1,3]dioxole-3a(6H)-carboxylate II-40

Methyl (3a*S*,4*R*,5*R*,7a*R*)-4,5-dihydroxy-2,2-dimethyl-5,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate II-42





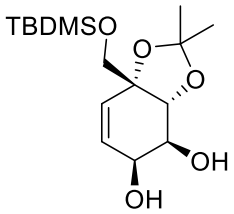
Methyl ester **II-13** (0.476 g, 2.27 mmol, 1.0 equiv.) was dissolved in acetone (10 mL) and NMO (0.319 g, 2.72 mmol, 1.2 equiv.) was added. Water (~1 mL) was added until full dissolution of NMO was

observed, then OsO_4 (2.5 wt% in *t*BuOH, 0.58 mL, 56.8 µmol, 2.5 mol%) added. The solution was stirred at RT for 16 h. Aqueous sodium thiosulfate (20 mL, 0.5 M) was added to quench the reaction and the product extracted with EtOAc (3 x 20 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum to give a dark brown oil. This oil was purified by flash column chromatography (0% MeOH, 100% CH_2Cl_2 → 3% MeOH, 97% CH_2Cl_2) using a Reveleris™ column cartridge (40 µm, 12 g silica, 30 mL/min) to give a pure faction of major diol **II-40** (0.229 g, 0.938 mmol, 41%) and a mixed faction of both **II-40** and **II-42**. The mixed faction was again subjected to purification by flash column chromatography (30% EtOAc, 70% petroleum ether → 50% EtOAc, 50% petroleum ether) using a GraceResolv™ column cartridge (12 g silica, 28 mL/min) to give a mixed faction of **II-40** and **II-42** (52 mg) and a pure faction of minor diol **II-42** (34 mg, 0.139 mmol, 6%).

Data for **II-40**. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.87 (1H, ddd, J = 10.4, 2.3, 1.3 Hz), 5.70 (1H, dt, J = 10.3, 1.9 Hz), 4.59 (1H, dd, J = 4.1, 1.6 Hz), 4.32-4.19 (2H, m), 3.83 (3H, s), 3.59 (1H, d, J = 7.5 Hz, O**H**), 3.02 (1H, d, J = 9.5 Hz, O**H**), 1.42 (3H, s), 1.38 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.3, 132.3, 125.3, 111.3, 77.5, 68.7, 65.2, 53.8, 27.7, 26.2. Data are in agreement with those previously reported.[17]

Data for **II-42**. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.93 (1H, dd, J = 10.3, 2.7 Hz), 5.90 (1H, ddd, J = 10.3, 3.4, 1.2 Hz), 4.97 (1H, dd, J = 3.3, 1.1 Hz), 4.39-4.31 (1H, m), 4.21 (1H, t, J = 4.9 Hz), 3.84 (3H, s), 3.17 (1H, d, J = 9.5 Hz, O**H**), 3.09 (1H, d, J = 5.5 Hz, O**H**), 1.44 (3H, s), 1.37 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 173.3, 131.1, 126.1, 111.5, 84.2, 73.8, 72.4, 66.0, 53.3, 27.8, 26.5. Data are in agreement with those previously reported.[17]

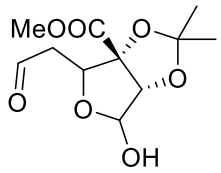
(3a*R*,4*S*,5*S*,7a*R*)-7a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxole-4,5-diol II-43



Diene **II-33** (0.325 g, 1.10 mmol, 1.0 equiv.) was dissolved in acetone (15 mL) and NMO (0.155 g, 1.32 mmol, 1.2 equiv.) was added. Water (~0.5 mL) was added until full dissolution of NMO was observed. OsO_4 (2.5 wt% in *t*BuOH, 0.28 mL, 27.5 µmol, 2.5 mol%) was then added. The solution was stirred at RT for 16 h. Aqueous sodium thiosulfate (1.0 M, 20 mL) was added to quench the reaction and the product extracted with EtOAc (3 x 20 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The product was purified by column chromatography (20% EtOAc, 80% petroleum ether) to give **II-43** as a colourless oil (0.331 g, 1.00 mmol, 91%).

R_f = 0.33 (20% EtOAc, 80% petroleum ether); $[\alpha]_D^{25}$ = -14.5 (CH_2Cl_2, *c*. 2 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.81 (1H, dt, J = 10.4, 1.7 Hz), 5.43 (1H, dt, J = 10.5, 2.1 Hz), 4.30 (1H, dd, J = 3.6, 1.8 Hz), 4.28-4.22 (1H, m), 4.20-4.13 (1H, m), 4.13 (1H, d, J = 10.5 Hz, O**H**), 3.74 (1H, d, J = 9.4 Hz), 3.62 (1H, d, J = 9.4 Hz), 2.79 (1H, d, J = 10.1 Hz, O**H**), 1.36 (3H, s), 1.36 (3H, s), 0.89 (9H, s), 0.11 (3H, s), 0.10 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 132.6, 128.3, 109.4, 80.7, 78.7, 68.3, 67.9, 65.4, 27.8, 27.2, 25.9, 18.4, -5.5, -5.5; ν_{max} (film) 3408, 2955, 2930, 2858, 1472, 1370, 1251, 1070, 833 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{30}O_5SiNa)^+$ 353.1755, found 353.1778.

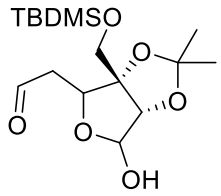
Methyl (3a*S*,6a*S*)-6-hydroxy-2,2-dimethyl-4-(2-oxoethyl)dihydrofuro[3,4-d][1,3]dioxole-3a(4H)-carboxylate II-39



Diol **II-40** (0.368 g, 1.51 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and water (2.0 mL). $NaIO_4$ (0.645 g, 3.02 mmol, 2.0 equiv.) was added and the solution stirred for 16 hours. Aqueous sodium thiosulfate (1.0 M, 20 mL) was added and the product extracted with EtOAc (3 x 20 mL). Organic phases were combined and dried over $MgSO_4$. The solvent was removed under vacuum to give **II-39** as a colourless oil (0.240 g, 0.923 mmol, 61%). Obtained product was of good purity and was found to be unstable on silica.

$[\alpha]_D^{25}$ = +16 (CH_2Cl_2, *c.* 1.0 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.77 (1H, t, J = 1.1 Hz), 5.38 (1H, d, J = 5.5 Hz), 4.89 (1H, t, J = 6.4 Hz), 4.76 (1H, s), 3.89 (3H, s), 3.17 (1H, d, J = 5.5 Hz, O**H**), 2.94-2.86 (2H, m), 1.51 (3H, s), 1.37 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 199.2, 172.2, 115.4, 100.7, 90.3, 90.1, 78.1, 53.4, 43.4, 26.6, 25.4; ν_{max} (film) 3452, 2991, 2955, 1725, 1438, 1378, 1261, 1077 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{11}H_{16}O_7Na)^+$ 283.0792, found 283.0788.

2-((3a*S*,6a*S*)-3a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)acetaldehyde II-44

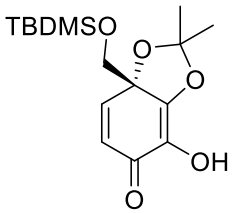


Diol **II-43** (0.252 g, 0.763 mmol, 1.0 equiv.) was dissolved in THF (8.0 mL) and water (2.0 mL). $NaIO_4$ (0.326 g, 1.53 mmol, 2.0 equiv.) was added and the solution stirred for 16 hours. Aqueous sodium thiosulfate (1.0 M, 10 mL) was added and the product extracted with EtOAc (3 x 10 mL). Organic phases

were combined and dried over $MgSO_4$. The solvent was removed under vacuum to give **II-44** as a colourless oil (0.228 g, 0.659 mmol, 86%). Obtained product was of good purity and was found to be unstable on silica.

$[\alpha]_D^{24}$ = +25 (CH_2Cl_2, *c.* 0.44 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.80 (1H, t, J = 1.5 Hz), 5.27 (1H, d, J = 6.8 Hz), 4.55 (1H, t, J = 6.4 Hz), 4.39 (1H, s), 3.91 (1H, d, J = 10.0 Hz), 3.82 (1H, d, J = 6.8 Hz, O**H**), 3.73 (1H, d, J = 9.9 Hz), 2.81 (1H, t, J = 1.4 Hz), 2.80 (1H, t, J = 1.3 Hz), 1.47 (3H, s), 1.36 (3H, s), 0.92 (9H, s), 0.13 (3H, s), 0.13 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 200.3, 113.6, 99.4, 90.3, 88.3, 75.4, 65.2, 44.7, 26.9, 26.6, 26.0, 18.5, -5.4, -5.4; ν_{max} (film) 3443, 2959, 2932, 2858, 1727, 1464, 1372, 1253, 1098, 779 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{30}O_6SiNa)^+$ 369.1704, found 369.1740.

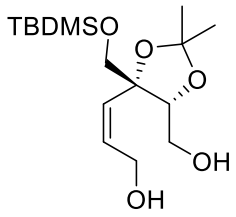
(*R*)-7a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-2,2-dimethylbenzo[d][1,3]dioxol-5(7aH)-one II-45



Diol **II-43** (80 mg, 0.242 mmol, 1.0 equiv.) and NMO (28 mg, 0.239 mmol, 0.99 equiv.) were dissolved in anhydrous CH_2Cl_2 (4.0 mL) and TPAP (5 mg, 14.2 µmol, 6 mol%) was added. The solution was stirred for 3 hours and then filtered through a pad of Celite. The solvent was removed and the product purified by column chromatography (20% EtOAc, 80% petroleum ether) to give **II-45** as a yellow oil (22 mg, 67.5 µmol, 28%).

R_f = 0.50 (20% EtOAc, 80% petroleum ether); $[\alpha]_D^{25}$ = +107 (CH_2Cl_2, *c*. 0.67 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.88 (1H, d, J = 9.8 Hz), 6.22 (1H, d, J = 9.8 Hz), 5.67 (1H, s, O**H**), 3.66 (1H, d, J = 9.3 Hz), 3.63 (1H, d, J = 9.3 Hz), 1.72 (3H, s), 1.49 (3H, s), 0.82 (9H, s), 0.00 (3H, s), -0.01 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 183.4, 147.8, 142.8, 128.7, 128.2, 118.9, 84.3, 68.9, 29.2, 27.6, 25.8, 18.3, -5.4, -5.5; ν_{max} (film) 3369, 2958, 2930, 2858, 1647, 1599, 1461, 1375, 1147, 1115 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{26}O_5SiH)^+$ 327.1622, found 327.1652.

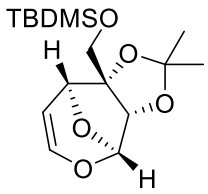
(*Z*)-3-((4R,5R)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol II-47



Diol **II-43** (0.129 g, 0.391 mmol, 1.00 equiv.) and $Pb(OAc)_4$ (0.182 g, 0.410 mmol, 1.05 equiv.) were dissolved in anhydrous MeCN (5.0 mL) and stirred for 50 minutes. The suspension was then filtered and the solvent was removed under vacuum. Pentane (10 mL) was added, the suspension filtered once more and the solvent again removed. The resulting material (0.023 g, 70.1 µmol, 1.00 equiv.) was immediately dissolved in MeOH (2.0 mL) and $NaBH_4$ (76 mg, 70.1 µmol, 10.0 equiv.) added. The solution was stirred for 5 hours. Saturated aqueous NH_4Cl (5.0 mL) was added and the product extracted with EtOAc (3 x 5.0 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **II-47** as a white solid (13 mg, 48.2 µmol, 12%).

R_f = 0.36 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = +16 (CH_2Cl_2, *c*. 0.5 g/100 mL); melting point = 49-51°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.80 (1H, dt, J = 12.5, 5.7 Hz), 5.53 (1H, dt, J = 12.5, 1.7 Hz), 4.41 (1H, ddd, J = 14.6, 5.5, 1.9 Hz), 4.30-4.23 (2H, m), 3.80-3.76 (2H, m), 3.69 (1H, d, J = 9.9 Hz), 3.66 (1H, d, J = 9.9 Hz), 2.75 (1H, s, O**H**), 2.33 (1H, s, O**H**), 1.48 (3H, s), 1.42 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 133.6, 128.0, 109.4, 84.5, 81.8, 68.6, 62.2, 59.8, 27.8, 27.2, 26.0, 18.5, -5.3, -5.4; ; ν_{max} (film) 3382, 2958, 2930, 2858, 1464, 1380, 1252, 1081 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{32}O_5SiNa)^+$ 355.1911, found 355.1942.

***tert*-Butyl(((3a*S*,4*S*,8*S*,8a*S*)-2,2-dimethyl-3a,4-dihydro-4,8-epoxy[1,3]dioxolo[4,5-c]oxepin-8a(8H)-yl)methoxy)dimethylsilane II-48**



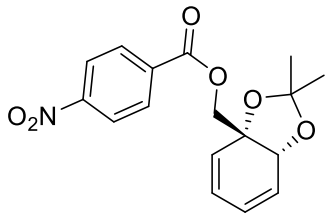
To diol **II-43** (62 mg g, 0.188 mmol, 1.0 equiv.) and $Pb(OAc)_4$ (83 mg, 0.188 mmol, 1.0 equiv.) was added anhydrous MeCN (4.0 mL). The suspension was stirred for 16 hours. Following this period, the suspension was filtered and the solvent removed under vacuum. ^{1}H NMR of the crude product showed a majority of **II-48** as the product, with a small quantity of a dialdehyde. The crude product was purified by column chromatography (5% EtOAc, 95% petroleum ether) to give **II-48** as a white solid (32 mg,

97.5 µmol, 52%). Crystals of the product were grown and X-ray crystallography was used to determine its absolute stereochemistry.

R_f = 0.25 (5% EtOAc, 95% petroleum ether); $[\alpha]_D^{25}$ = +17 (CH_2Cl_2, *c*. 1 g/100 mL); melting point = 43-45°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.19 (1H, d, J = 6.0 Hz), 5.40 (1H, d, J = 1.2 Hz), 5.10 (1H, ddd, J = 5.8, 5.1, 0.6 Hz), 4.49 (1H, d, J = 0.5 Hz), 4.39 (1H, ddd, J = 5.1, 1.2, 0.6 Hz), 4.06 (1H, d, J = 10.8 Hz), 3.98 (1H, d, J = 10.8 Hz), 1.48 (3H, s), 1.41 (3H, s), 0.90 (9H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.2, 114.8, 103.9, 103.7, 100.6, 88.6, 79.0, 65.3, 28.7, 28.2, 26.0, 18.5, -5.2, -5.3; ν_{max} (film) 2955, 2930, 2858, 1636, 1463, 1380, 1239, 1211, 1112, 1061 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{28}O_5SiNa)^+$ 351.1598, found 355.1622.

Crystal structure data for **II-48** to be found in the appendix.

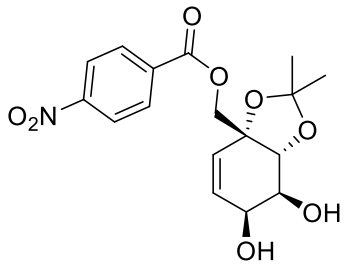
((3a*R*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methyl 4-nitrobenzoate II-50



A solution of alcohol **II-49** (0.131 g, 0.719 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (3 mL) was cooled to 0°C. NEt_3 (0.12 mL, 0.863 mmol, 1.2 equiv.) was then added, followed by a solution of 4-nitrobenzoyl chloride (0.147 g, 0.791 mmol, 1.1 equiv.) in CH_2Cl_2 (1 mL). The solution was allowed to warm to room temperature over 16 hours before brine (10 mL) was added to quench the reaction. The product was extracted with CH_2Cl_2 (2 x 10 mL). Organic layers were combined, washed with saturated aqueous $NaHCO_3$ (15 mL), dried over $MgSO_4$ and the solvent removed under vacuum. The resulting orange/yellow solid was purified by flash column chromatography (100% petroleum ether → 10% EtOAc, 90% petroleum ether) using a Reveleris™ column cartridge (4 g silica, 15 mL/minute) to give **II-50** as a white solid (0.148 g, 0.447 mmol, 62%).

R_f = 0.30 (10% EtOAc, 90% petroleum ether); $[\alpha]_D^{25}$ = -168 (CH_2Cl_2, *c*. 1 g/100 mL); melting point = 99-100°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.32-8.27 (2H, m), 8.21-8.17 (2H, m), 6.18-6.13 (1H, m), 6.11-6.04 (2H, m), 5.80 (1H, d, J = 9.9 Hz), 4.55 (1H, d, J = 4.5 Hz), 4.42 (1H, d, J = 11.4 Hz), 4.30 (1H, d, J = 11.4 Hz), 1.43 (3H, s), 1.39 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.4, 150.8, 135.3, 131.0, 128.1, 125.5, 124.7, 123.9, 123.8, 107.1, 78.4, 72.5, 67.7, 27.2, 26.7; ν_{max} (film) 3053, 2987, 2940, 1727, 1527, 1347, 1269, 1102, 844 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{17}H_{17}NO_6Na)^+$ 354.0948, found 354.0957.

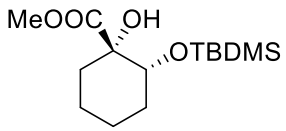
((3aR,6S,7S,7aR)-6,7-dihydroxy-2,2-dimethyl-7,7a-dihydrobenzo[d][1,3]dioxol-3a(6H)-yl)methyl 4-nitrobenzoate II-51



To a solution of diene **II-50** (0.146 g, 0.441 mmol, 1.0 equiv.) in acetone (3 mL) was added NMO (67 mg, 0.573 mmol, 1.3 equiv.). Water (~0.7 mL) was added slowly until full dissolution of NMO was observed. OsO_4 (2.5 wt% in *t*BuOH, 0.15 mL, 14.7 µmol, 3 mol%) was subsequently added dropwise. After stirring at room temperature for 16 hours, the reaction was quenched through the addition of sodium thiosulfate (1 M, 10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL). Organic layers were combined, washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product purified by flash column chromatography (100% petroleum ether → 50% EtOAc, 50% petroleum ether) using a Reveleris™ column cartridge (4 g silica, 15 mL/min) to give **II-51** as a white solid (0.106 g, 0.290 mmol, 66%).

R_f = 0.26 (50% EtOAc, 50% petroleum ether; $[\alpha]_D^{25}$ = +2 (CH_2Cl_2, *c*. 0.5 g/100 mL); melting point = 119-121°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.31-8.27 (2H, m), 8.26-8.21 (2H, m), 5.76 (1H, dt, J = 10.4, 1.8 Hz), 5.69 (1H, dt, J = 10.4, 1.9 Hz), 4.63 (1H, d, J = 11.6 Hz), 4.50-4.43 (1H, m), 4.42 (1H, dd, J = 4.4, 1.6 Hz), 4.40-4.35 (2H, m), 2.86 (1H, d, J = 3.2 Hz, O**H**), 2.60 (1H, d, J = 7.2 Hz, O**H**), 1.35 (3H, s), 1.34 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.6, 150.8, 135.4, 130.9, 130.0, 127.2, 123.8, 109.6, 78.1, 76.1, 69.0, 67.3, 65.7, 27.9, 27.4; ν_{max} (film) 3443, 2983, 1726, 1608, 1528, 1273, 1065, 839 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{17}H_{19}O_8NH)^+$ 388.1003, found 388.1025.

Methyl (1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxycyclohexane-1-carboxylate II-52

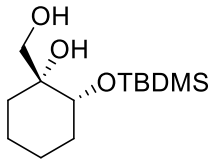


Diol **II-23** (0.368 g, 2.11 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (20 mL) and cooled to -78°C. Triethylamine (0.59 mL, 4.23 mmol, 2.0 equiv.) was added dropwise followed by addition of TBDMSOTf (0.58 mL, 2.54 mmol, 1.2 equiv.). The reaction was stirred for 90 minutes and then quenched by addition of water (20 mL). The organic phase was collected and washed with brine (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$ and the solvent removed under vacuum. The crude

product was purified by column chromatography to give **II-52** as a colourless oil (0.535 g, 1.86 mmol, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.89 (1H, dd, J = 10.3, 5.3 Hz), 3.68 (3H, s), 3.00 (1H, d, J = 2.1 Hz), 1.95-1.15 (8H, m), 0.79 (9H, s), 0.00 (3H, s), -0.07 (3H, s). Data are in agreement with those previously reported.[12]

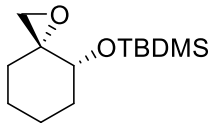
(1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-(hydroxymethyl)cyclohexan-1-ol II-53



Methyl ester **II-52** (0.535 g, 1.86 mmol, 1.0 equiv.) was dissolved in anhydrous THF (20 mL) and the solution cooled to -78°C. $LiBH_4$ (4.0 M, 1.0 mL, 4 mmol, 2.2 equiv.) was added dropwise. The solution was allowed to warm to RT over 16 hours. The reaction was then quenched through slow addition of EtOAc (20 mL) and water (20 mL). The organic phase was collected and the product further extracted with EtOAc (2 x 20 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed. The product was purified by column chromatography (20% EtOAc, 80% petroleum ether) to give **II-53** as a colourless oil (0.374 g, 1.44 mmol, 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ =3.73-3.50 (2H, m), 3.37 (1H, dd, J = 11.2, 5.4 Hz), 2.44 (1H, d, J = 1.6 Hz, O**H**), 2.12 (1H, s, O**H**), 1.91-1.06 (8H, m), 0.89 (9H, s), 0.08 (6H, s). Data are in agreement with those previously reported.[12]

(((3*R*,4*R*)-1-Oxaspiro[2.5]octan-4-yl)oxy)(*tert*-butyl)dimethylsilane II-54

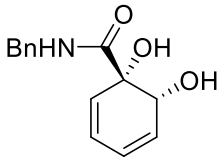


To a 0°C stirred solution of diol **II-53** (0.374 g, 1.44 mmol, 1.0 equiv.), DMAP (0.018 g, 0.144 mmol, 10 mol%) and triethylamine (1.0 mL, 7.19 mmol, 5.0 equiv.) in CH_2Cl_2 (3 mL) was added *p*TsCl (0.380 g in CH_2Cl_2, 2.01 mmol, 1.4 equiv.) dropwise. The solution was allowed to warm to RT over 20 hours. Ice water (10 mL) was added to the solution, and the resulting biphasic solution was stirred vigorously for 1 hour. The biphasic solution was extracted with EtOAc (3 x 15 mL). Organic phases were combined and washed with water (20 mL), cold aqueous HCl (1.0 M, 20 mL), water (20 mL), aqueous saturated $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). Organic phases were dried over $MgSO_4$ and the solvent removed under vacuum. The product was re-dissolved in MeOH (4.0 mL), cooled to 0°C and K_2CO_3 (0.199 g, 1.44 mmol, 1.0 equiv.) was added. The solution was stirred at 0°C for 1 hour and then

allowed to warm to RT over 1 hour. The solvent was removed under vacuum. CH_2Cl_2 (5 mL) was added to the resulting product, the suspension filtered and the solvent again removed under vacuum. The crude product was purified by column chromatography (10% EtOAc, 90% petroleum ether) to give **II-54** as a colourless oil (0.144 g, 0.594 mmol, 41%).

R_f = 0.28 (20% EtOAc, 80% petroleum ether); $[\alpha]_D^{25}$ = -23 ($CHCl_3$, *c*. 1 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.50 (1H, dd, J = 6.1, 3.0 Hz), 2.71 (1H, dd, J = 5.1, 1.2 Hz), 2.55 (1H, d, J = 5.1 Hz), 1.98 (1H, ddd, J = 13.1, 9.9, 4.3 Hz), 1.82-1.68 (3H, m), 1.67-1.57 (1H, m), 1.52-1.36 (2H, m), 1.33-1.23 (1H, m), 0.90 (9H, s), 0.08 (3H, s), 0.04 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 72.1, 61.4, 51.9, 34.1, 30.1, 26.0, 24.9, 21.1, 18.3, -4.5, -4.8; ν_{max} (neat) 2934, 2857, 1462, 1446, 1250, 1052, 835 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{13}H_{26}O_2SiNa)^+$ 265.1594, found 265.1582.

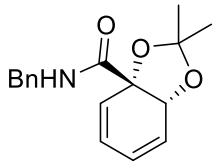
(1*S*,6*R*)-*N*-benzyl-1,6-dihydroxycyclohexa-2,4-diene-1-carboxamide II-55



A solution of diol acid **II-06** (0.237 g, 1.52 mmol, 1.0 equiv.) in EtOAc (20 mL) was cooled to 0°C. T3P® (50% in EtOAc, 0.99 mL, 1.67 mmol, 1.1 equiv.) and freshly distilled benzylamine (0.28 mL, 2.58 mmol, 1.7 equiv.) were added slowly. After stirred for 5 minutes at 0°C, NMM (0.50 mL, 4.56 mmol, 3.0 equiv.) was added slowly. At this point, bubbling was observed in the solution. The solution was warmed to RT over 72 hours, during which a white precipitate formed in solution. Water (30 mL) was added and the product extracted with EtOAc (3 x 25 mL). Organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$ and the solvent removed under vacuum to give an oil. ^{1}H NMR of the crude product indicated phenol, NMM and unreacted benzylamine as the predominant components of the mixture. Purification by column chromatography (50% EtOAc, 50% petroleum ether → 75% EtOAc, 25% petroleum ether) gave **II-55** as a white solid (12 mg, 49.0 µmol, 3%).

R_f = 0.13 (50% EtOAc, 50% petroleum ether; $[\alpha]_D^{25}$ = -141 (CH_2Cl_2, *c*. 0.44 g/100 mL); melting point = 133-136°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.31 (2H, m), 7.31-7.25 (3H, m), 7.13 (1H, m, N**H**), 6.14 (1H, dd, J = 9.5, 5.2 Hz), 6.00-5.94 (1H, m), 5.87 (1H, dd, J = 9.7, 2.5 Hz), 5.79 (1H, d, J = 9.5 Hz), 4.99 (t, J = 2.5 Hz), 4.52 (1H, dd, J = 14.9, 6.0 Hz), 4.46 (1H, dd, J = 14.9, 5.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.7, 137.8, 131.8, 128.9, 127.8, 127.7, 127.3, 127.0, 123.1, 75.2, 70.6, 43.9; ν_{max} (film) 3384, 3312, 3044, 2925, 2898, 1660, 1533, 1373, 1106, 1011, 720 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{14}H_{15}O_3NNa)^+$ 268.0944, found 268.0944.

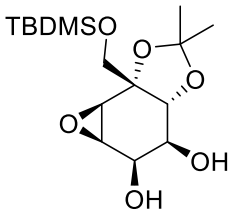
(3a*S*,7a*R*)-*N*-benzyl-2,2-dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxamide II-57



Acid **II-07** (0.440 g, 2.24 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (20 mL). DCC (0.485 g, 2.35 mmol, 1.05 equiv.), DMAP (27 mg, 0.224 mmol, 10 mol%) and freshly distilled benzylamine (0.26 mL, 2.35 mmol, 1.05 equiv.) were then added. The solution was stirred for 16 hours. The suspension was filtered and the solvent removed under vacuum. The resulting heterogeneous oil/solid was purified by column chromatography (25% EtOAc, 75% petroleum ether) to give **II-57** as an off white solid (0.352 g, 1.23 mmol, 55%).

R_f = 0.28 (20% EtOAc, 80% petroleum ether); $[\alpha]_D^{25}$ = -278 (CH_2Cl_2, *c*. 1 g/100 mL); MP 73-76°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 (2H, tt, J = 7.0, 1.2 Hz), 7.31-7.26 (3H, m), 7.02 (1H, t, J = 6.9 Hz, N**H**), 6.17-6.10 (2H, m), 6.04-5.99 (1H, m), 5.72-5.66 (1H, m), 4.93 (1H, d, J = 4.2 Hz), 4.48 (1H, dd, J = 14.0, 5.9 Hz), 4.45 (1H, dd, J = 14.0, 5.9 Hz), 1.40 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 172.5, 138.0, 128.9, 127.8, 127.8, 125.5, 125.1, 124.6, 124.1, 107.2, 80.5, 73.9, 43.5, 27.1, 25.8; ν_{max} (film) 3366, 2987, 2931, 1668, 1525, 1247, 1056, 867, 701 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{17}H_{19}O_3NNa)^+$ 308.1257, found 308.1241.

(3a*R*,4*S*,5*R*,5a*R*,6a*R*,6b*S*)-6b-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethylhexahydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxole-4,5-diol II-59

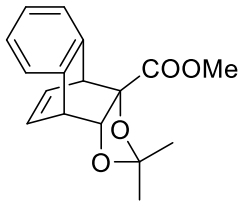


Diol **II-43** (55 mg, 0.167 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (3.0 mL) and *m*CPBA (34 mg, 0.200 mmol, 1.2 equiv.) was added. The solution was stirred for 1 day and a further quantity of *m*CPBA added (34 mg, 0.200 mmol, 1.2 equiv.). After stirring for another 2 days, the reaction was quenched with aqueous sodium thiosulfate (1.0 M, 10 mL). The product was extracted with CH_2Cl_2 (3 x 10 mL). Organic phases were combined and washed with aqueous saturated $NaHCO_3$ (20 mL). The organic phase was dried over $MgSO_4$ and the solvent removed to give **II-59** as a white solid (51 mg, 0.147 mmol, 88%). The crude product was found to be of good purity.

R_f = 0.34 (30% EtOAc, 70% petroleum ether); $[\alpha]_D^{25}$ = -11 (CH_2Cl_2, *c*. 2 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.34 (1H, dd, J = 3.8, 2.0 Hz), 4.23-4.19 (1H, m), 4.03 (1H, dtd, J = 11.5, 4.0, 1.5 Hz), 3.87 (1H,

d, J = 10.7 Hz), 3.81 (1H, d, J = 10.7 Hz), 3.44 (1H, dt, J = 4.1, 1.5 Hz), 3.28 (1H, dd, J = 4.1, 2.0 Hz), 3.03 (1H, d, J = 11.7 Hz), 2.93 (1H, s), 1.40 (3H, s), 1.37 (3H, s), 0.92 (3H, s), 0.11 (3H, s), 0.11 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 109.6, 78.6, 78.6, 68.0, 67.4, 64.7, 57.4, 55.9, 28.0, 26.3, 26.0, 18.6, -5.4, -5.4; ν_{max} (film) 3466, 2988, 2954, 2930, 2857, 1381, 1372, 1078, 835 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{30}O_6SiNa)^+$ 369.1704, found 369.1725.

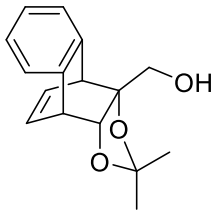
Methyl (3a*S*,4*S*,9*R*,9a*R*)-2,2-dimethyl-9,9a-dihydro-4,9-ethenonaphtho[2,3-d][1,3]dioxole-3a(4H)-carboxylate II-61



To a solution of diene **II-13** (0.166 g, 0.790 mmol, 1.0 equiv.) in MeCN (4.0 mL) was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.38 mL, 1.58 mmol, 2.0 equiv.). CsF (0.480 g, 3.16 mmol, 4.0 equiv.) was then added and the suspension stirred for 16 hours. After this time, water (20 mL) was added and the product extracted with Et_2O (3 x 15 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum to give an orange oil. This crude product was purified by column chromatography (5% EtOAc, 95% petroleum ether → 10% EtOAc, 90% petroleum ether) to give **II-61** as a colourless oil (0.205 g, 0.716 mmol, 91%).

R_f = 0.41 (10% EtOAc, 90% petroleum ether); $[\alpha]_D^{25}$ = -12 (CH_2Cl_2, *c*. 0.5 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.25 (1H, d, J = 7.3 Hz), 7.15-7.07 (3H, m), 6.58 (1H, t, J = 6.5 Hz), 6.52 (1H, ddd, J = 7.6, 6.1, 1.6 Hz), 4.87 (1H, d, J = 3.7 Hz), 4.32 (1H, dd, J = 6.0, 1.4 Hz), 4.20 (1H, ddd, J = 5.5, 3.7, 1.6 Hz), 3.61 (3H, s), 1.42 (3H, s), 1.26 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 172.0, 139.9, 138.8, 134.4, 132.1, 126.8, 126.6, 125.1, 125.0, 113.9, 89.2, 82.0, 52.6, 48.2, 46.0, 26.3, 26.3; ν_{max} (film) 2988, 2952, 1737, 1373, 1250, 1206, 1064, 709 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{17}H_{18}O_4Na)^+$ 309.1097, found 309.1104.

((3a*R*,4*S*,9*R*,9a*R*)-2,2-Dimethyl-9,9a-dihydro-4,9-ethenonaphtho[2,3-d][1,3]dioxol-3a(4H)-yl)methanol II-62

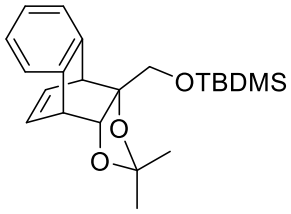


Methyl ester **II-61** (0.195 g, 0.682 mmol, 1.0 equiv.) was dissolved in anhydrous THF (5.0 mL). The solution was cooled to 0°C and $LiAlH_4$ (2.4 M solution in THF, 0.52 mL, 1.25 mmol, 1.8 equiv.) added

dropwise. After allowing to warm to RT over 6 hours, the reaction was cooled to 0°C and quenched through slow addition of water (15 mL). The suspension was filtered and the product extracted from the filtrate using EtOAc (3 x 15 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (50% EtOAc, petroleum ether) to give **II-62** as a colourless oil (0.100 g, 0.390 mmol, 57%).

R_f = 0.53 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = +15 (CH_2Cl_2, *c*. 1 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.28-7.24 (1H, m), 7.22-7.19 (1H, m), 7.13-7.10 (1H, m), 6.58-6.54 (2H, m), 4.32 (1H, dd, J = 4.4, 3.2 Hz), 4.14 (1H, q, J = 3.7 Hz), 3.95 (1H, d, J = 3.6 Hz), 3.53 (1H, d, J = 11.6 Hz), 2.98 (1H, d, J = 11.6 Hz), 1.90 (1H, s, O**H**), 1.43 (3H, s), 1.38 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.6, 139.2, 134.1, 133.9, 126.7, 126.4, 125.3, 125.0, 113.4, 90.5, 83.1, 67.6, 46.7, 46.6, 28.8, 27.2; ν_{max} (film) 3461, 3062, 2984, 2936, 1459, 1369, 1245, 1208, 1064, 718 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{18}O_3Na)^+$ 281.1148, found 281.1147.

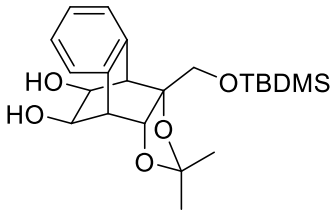
***tert*-Butyl(((3a*R*,4*S*,9*R*,9a*R*)-2,2-dimethyl-9,9a-dihydro-4,9-ethenonaphtho[2,3-d][1,3]dioxol-3a(4H)-yl)methoxy)dimethylsilane II-63**



Alcohol **II-62** (87 mg, 0.337 mmol, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (4.0 mL) and the solution cooled to -78°C. Triethylamine (70 µL, 0.506 mmol, 1.5 equiv.) and TBDMSOTf (90 µL, 0.388 mmol, 1.2 equiv.) were added dropwise. The solution was allowed to warm to RT over 24 hours, at which point water (5.0 mL) was added. The organic phase was collected, and the aqueous phase further extracted with CH_2Cl_2 (2 x 5.0 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (5% EtOAc, 95% petroleum ether) to give **II-63** as a colourless oil (0.112 g, 0.301 mmol, 89%).

R_f = 0.58 (5% EtOAc, 95% petroleum ether); $[\alpha]_D^{25}$ = -1.0 (CH_2Cl_2, *c*. 2 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.20-7.17 (2H, m), 7.12-7.07 (2H, m), 6.58-6.51 (2H, m), 4.29 (1H, dd, J = 5.7, 1.9 Hz), 4.13 (1H, ddd, J = 5.5, 3.6, 2.0 Hz), 3.96 (1H, d, J = 3.6 Hz), 3.50 (1H, d, J = 10.8 Hz), 3.01 (1H, d, J = 10.8 Hz), 1.41 (3H, s), 1.37 (3H, s), 0.87 (9H, s), -0.04 (3H, s), -0.04 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 142.3, 139.4, 134.2, 134.0, 126.3, 126.1, 125.1, 124.9, 113.3, 91.2, 82.3, 68.6, 46.9, 46.9, 28.5, 27.4, 26.1, 18.6, -5.3, -5.4; ν_{max} (film) 2955, 2930, 2857, 1472, 1461, 1250, 1094, 777 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{22}H_{32}O_3SiNa)^+$ 395.2013, found 395.2030.

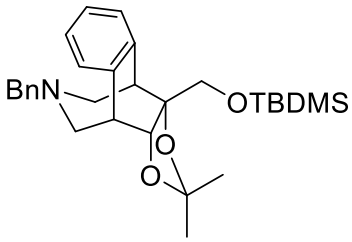
(3a*R*,4*S*,9*R*,9a*R*,10*S*,11*R*)-9a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-ethanonaphtho[2,3-d][1,3]dioxole-10,11-diol II-64



Alkene **II-63** (0.175 g, 0.470 mmol, 1.0 equiv.) was dissolved in acetone (5.0 mL) and NMO added (83 mg, 0.705 mmol, 1.5 equiv.). Water (~0.2 mL) was then added until full dissolution of NMO was observed. OsO_4 (2.5 wt% in BuOH, 0.24 mL, 23.5 µmol, 5 mol%) was added and the solution heated to 45°C for 16 hours. After allowing to cool to RT, aqueous sodium thiosulfate (1.0 M, 15 mL) was added and the product extracted with EtOAc (3 x 15 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (5% EtOAc, 95% petroleum ether → 50% EtOAc, 50% petroleum ether) to give **II-64** as a colourless oil (0.128 g, 0.315 mmol, 67%).

R_f = 0.47 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = -14 (CH_2Cl_2, *c*. 1 g/100 mL); ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 7.28-7.22 (4H, m), 4.64-4.59 (1H, m), 4.54-4.50 (1H, m), 3.83 (1H, d, J = 4.4 Hz), 3.55 (1H, d, J = 2.8 Hz), 3.54 (1H, dd, J = 4.4, 3.3 Hz), 3.38 (1H, d, J = 10.9 Hz), 2.88 (1H, d, J = 10.9 Hz), 2.08-2.03 (1H, m, O**H**), 1.94-1.88 (1H, m, O**H**), 1.51 (3H, s), 1.39 (3H, s), 0.87 (9H, s), -0.05 (3H, s), -0.06 (3H, s); ^{13}C NMR (126 MHz, CD_2Cl_2) δ = 138.1, 135.6, 128.8, 128.5, 128.2, 127.9, 112.3, 87.0, 78.1, 68.4, 66.0, 49.0, 48.2, 27.5, 27.5, 26.2, 18.8, -5.3, -5.3; ν_{max} (film) 3389, 2957, 2930, 2857, 1463, 1371, 1254, 1061 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{22}H_{34}O_5SiNa)^+$ 429.2068, found 429.2084.

(3a*R*,4*R*)-11-Benzyl-3a-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-(methanoiminomethano)naphtho[2,3-d][1,3]dioxole II-65

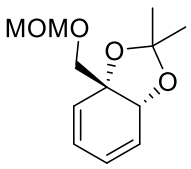


Diol **II-64** (59 mg, 0.145 mmol, 1.0 equiv.) and $NaIO_4$ (62 mg, 0.290 mmol, 2.0 equiv.) were dissolved in THF (4.0 mL) and water (0.4 mL) and stirred for 3 h. The reaction was quenched with aqueous sodium thiosulfate (1.0 M, 15 mL) and the product extracted with EtOAc (3 x 15 mL). Organic phases were combined, dried of $MgSO_4$ and the solvent removed under vacuum. The product was immediately re-dissolved in anhydrous CH_2Cl_2 (4.0 mL) and freshly distilled benzylamine (16 µL, 0.152 mmol, 1.05

equiv.) added. The solution was stirred for 1 hour, after which sodium triacetoxyborohydride (0.154 g, 0.725 mmol, 5.0 equiv.) was added. After stirred for 16 hours, the reaction was quenched through slow addition of water (8.0 mL). The product was extracted with CH_2Cl_2 (3 x 8.0 mL). Organic phases were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (2.5% EtOAc, 97.5% petroleum ether) to give **II-65** as a pale yellow oil (33 mg, 68.9 µmol, 48%).

R_f = 0.54 (2.5% EtOAc, 97.5% petroleum ether); $[\alpha]_D^{25}$ = +4.0 (CH_2Cl_2, *c*. 0.5 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.25-7.08 (7H, m), 6.98-6.94 (2H, m), 3.98 (1H, d, J = 6.5 Hz), 3.58 (1H, d, J = 14.3 Hz), 3.55 (1H, d, J = 14.4 Hz), 3.39 (1H, d, J = 10.8 Hz), 3.35 (1H, d, J = 8.4 Hz), 3.30 (1H, t, J = 6.9 Hz), 3.12 (1H, d, J = 11.5 Hz), 3.02 (1H, d, J = 10.8 Hz), 2.96 (1H, d, J = 12.1 Hz), 2.70 (1H, t, J = 10.3 Hz), 2.59 (1H, dd, J = 11.5, 7.5 Hz), 1.46 (3H, s), 1.45 (3H, s), 0.83 (9H, s), -0.07 (3H, s), -0.10 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 140.3, 138.8, 137.4, 128.8, 128.1, 127.4, 127.1, 127.0, 126.8, 126.7, 111.5, 87.6, 78.7, 69.1, 61.8, 50.0, 49.5, 44.2, 43.8, 30.5, 28.0, 26.9, 26.1, 18.6, -5.3, -5.4; ν_{max} (film) 2927, 2856, 1459, 1378, 1256, 1109, 1083, 750 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{29}H_{41}O_3NSiH)^+$ 480.2928, found 480.2939.

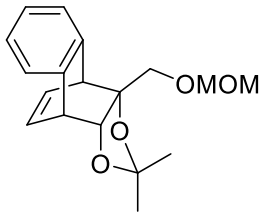
(3a*R*,7a*R*)-3a-((Methoxymethoxy)methyl)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole II-66



Alcohol **II-49** (1.77 g, 9.7 mmol, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to 0°C. Following addition of DIPEA (3.3 mL, 19.4 mmol, 2.0 equiv.) and MOMCl (2.2 mL, 29.1 mmol, 3.0 equiv.), the reaction was stirred at 0°C for 1 hour and then allowed to warm to room temperature of 5 hours. Water (20 mL) was added and the organic phase collected. The aqueous phase was further extracted with CH_2Cl_2 (20 mL). Combined organic phases were washed with aqueous saturated $NaHCO_3$ (30 mL) and brine (30 mL) before being dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (10% EtOAc, 90% petroleum ether) to give **II-66** as a colourless oil (1.62 g, 7.16 mmol, 74%).

R_f = 0.76 (23% EtOAc, 77% petroleum ether); $[\alpha]_D^{25}$ = -184 (CH_2Cl_2, *c.* 1.0 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.09 (1H, dd, J = 9.6, 5.3 Hz), 6.04-5.95 (2H, m), 5.79 (1H, d, J = 9.8 Hz), 4.66 (1H, d, J = 6.5 Hz), 4.64 (1H, d, J = 6.5 Hz), 4.47 (1H, d, J = 4.5 Hz), 3.56 (1H, d, J = 10.3 Hz), 3.44 (1H, d, J = 10.4 Hz), 3.35 (3H, s), 1.44 (3H, s), 1.37 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 129.3, 125.3, 124.8, 122.7, 106.5, 96.9, 79.4, 72.3, 71.1, 55.5, 27.3, 26.8; ν_{max} (film) 2985, 2935, 2883, 1459, 1376, 1106, 919 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{12}H_{18}O_4Na)^+$ 249.1097, found 249.1126.

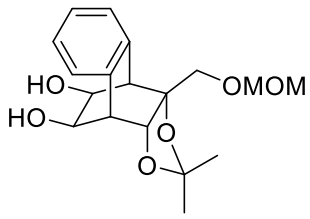
(3a*R*,4*S*,9*R*,9a*R*)-3a-((Methoxymethoxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-ethenonaphtho[2,3-d][1,3]dioxole II-67



To a solution of diene **II-66** (0.100 g, 0.442 mmol, 1.0 equiv.) in MeCN (10 mL) was added CsF (0.402 g, 2.65 mmol, 6.0 equiv.) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (0.32 mL, 1.33 mmol, 3.0 equiv.). The reaction was stirred at room temperature for 16 hours. Water (10 mL) was added to the reaction and the aqueous phase extracted with Et_2O (2 x 20 mL). Combined organic phases were washed with brine (30 mL) and dried over $MgSO_4$. The solvent was then removed under vacuum and the crude product purified by column chromatography (10% EtOAc, 90% pentane) to give **II-67** as a yellow oil (75 mg, 0.248 mmol, 56%).

R_f = 0.64 (25% EtOAc, 75% hexane); $[\alpha]_D^{26}$ = +16 (CH_2Cl_2, *c*. 1.0 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.23-7.18 (2H, m), 7.14-7.08 (2H, m), 6.60-6.50 (2H, m), 4.64 (1H, d, J = 6.5 Hz), 4.57 (1H, d, J = 6.5 Hz), 4.35 (1H, dd, J = 5.6, 2.0 Hz), 4.14 (1H, ddd, J = 5.5, 3.6, 2.1 Hz), 3.97 (1H, d, J = 3.6 Hz), 3.50 (1H, d, J = 10.5 Hz), 3.34 (3H, s), 2.87 (1H, d, J = 10.5 Hz), 1.43 (3H, s), 1.40 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.9, 139.2, 134.0 , 126.5, 126.3, 125.1, 125.1, 113.6, 96.8, 89.7, 83.0, 72.3, 55.4, 47.0, 46.7, 28.5, 27.2; ν_{max} (film) 2985, 2935, 2883, 1709, 1459, 1376, 1209, 1039 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{18}H_{22}O_4Na)^+$ 325.1410, found 325.1431.

(3a*R*,4*S*,9*R*,9a*R*,10*S*,11*R*)-9a-((Methoxymethoxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-ethanonaphtho[2,3-d][1,3]dioxole-10,11-diol II-68

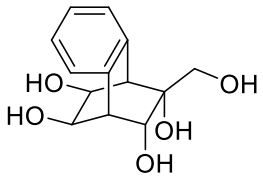


To a solution of alkene **II-67** (70 mg, 0.232 mmol, 1.0 equiv.) in acetone (3 mL) and water (3 mL) was added NMO (27 mg, 0.232 mmol, 1.0 equiv.). OsO_4 (2.5 wt% in *t*BuOH, 0.12 mL, 12 µmol, 5 mol%) was then added. The reaction was stirred at room temperature for 72 hours. Aqueous sodium thiosulfate (1.0 M, 10 mL) was added to quench the reaction and the product was extracted with EtOAc (3 x 10 mL). Organic layers were combined, washed with brine (20 mL) and dried over $MgSO_4$. The solvent

was removed and the crude product purified by column chromatography (75% EtOAc, 25% hexane) to give **II-68** as a white solid (32 mg, 95 µmol, 41%).

R_f = 0.53 (75% EtOAc, 25% petroleum ether); $[\alpha]_D^{26}$ = -10 (CH_2Cl_2, *c*. 1.5 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.29-7.24 (4H, m), 4.64 (1H, dd, J = 7.6, 3.2 Hz), 4.60 (1H, d, J = 6.5 Hz), 4.64 (1H, dd, J = 7.7, 2.8 Hz), 4.52 (1H, d, J = 6.5 Hz), 3.86 (1H, d, J = 4.4 Hz), 3.66 (1H, d, J = 2.8 Hz), 3.58 (1H, ddd, J = 4.4, 3.2, 1.1 Hz), 3.34 (1H, d, J = 10.6 Hz), 3.31 (3H, s), 2.80 (1H, d, J = 10.6 Hz), 1.54 (3H, s), 1.43 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 137.0, 134.7, 128.3, 128.3, 128.2, 127.9, 112.3, 96.8, 85.3, 78.4, 71.9, 65.5, 65.4, 55.5, 48.7, 47.5, 27.2, 27.2; ν_{max} (film) 3427, 3399, 2989, 2936, 2884, 1402, 1252, 1059, 754 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{18}H_{24}O_6Na)^+$ 359.1465, found 359.1592.

(1*S*,2*R*,3*R*,4*R*,9*S*,10*R*)-3-(Hydroxymethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2,3,9,10-tetraol II-69

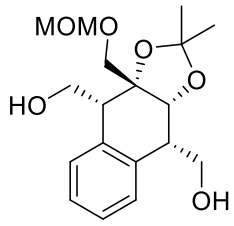


Diol **II-68** (30 mg, 89 µmol, 1.0 equiv.) was dissolved in MeOH (5 mL) and acidic ion exchange resin (DOWEX 50W-X8, 20-50 mesh) added. After stirring for 48 hours, the suspension was filtered and the solvent was removed under vacuum. The crude product was purified by recrystallisation with $CHCl_3$ to give **II-68** as a white solid (22 mg, 87 µmol, 98%).

$[\alpha]_D^{26}$ = +4 (MeOH, *c*. 0.5 g/100 mL); ^{1}H NMR (500 MHz, CD_3OD) δ = 7.23-7.17 (4H, m), 4.59 (1H, dd, J = 7.8, 3.4 Hz), 4.49 (1H, dd, J = 7.8, 2.2 Hz), 3.34 (1H, d, J = 3.4 Hz), 3.22 (1H, d, J = 3.2 Hz), 3.18 (1H, t, J = 2.9 Hz), 3.00 (1H, d, J = 11.3 Hz), 2.90 (1H, d, J = 11.2 Hz); ^{13}C NMR (126 MHz, CD_3OD) δ = 138.5, 138.1, 128.8, 128.1, 128.0, 127.8, 73.0, 70.4, 69.7, 66.3, 65.4, 51.9, 50.9; ν_{max} (film) 3454, 3233, 2960, 2889, 1484, 1360, 1127, 821 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{13}H_{16}O_5Na)^+$ 275.0890, found 275.0949.

Crystal structure data for **II-69** to be found in the appendix.

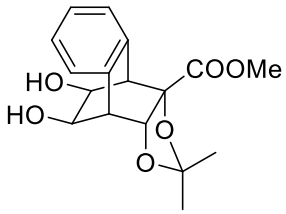
((3a*R*,4*R*,9*S*,9a*R*)-3a-((methoxymethoxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydronaphtho[2,3-d][1,3]dioxole-4,9-diyl)dimethanol II-70



To a solution of diol **II-68** (41 mg, 0.123 mmol, 1.0 equiv.) in MeOH (10 mL) and water (2 mL) was added $NaIO_4$ (1.09 g, 5.10 mmol, 24 equiv.). The solution was stirred at room temperature for 6 hours before addition of aqueous sodium thiosulfate (1.0 M, 20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and combined organic phases were dried over $MgSO_4$. After the solvent was removed under vacuum, the crude product was immediately re-dissolved in MeOH (10 mL). The solution was cooled to 0°C and $NaBH_4$ (45 mg, 1.20 mmol, 9.8 equiv.) added. The solution was allowed to warm to room temperature over 24 hours, at which point water (20 mL) was added and the aqueous phase extracted with EtOAc (3 x 20 mL). Organic phases were combined and washed with brine (30 mL). After drying over $MgSO_4$, the solvent was removed under vacuum. The crude product was purified by column chromatography (75% EtOAc, 25% hexane) to give **II-70** as a white solid (16 mg, 47 µmol, 38%).

R_f = 0.60 (75% EtOAc, 25% hexane); $[\alpha]_D^{25}$ = +20 ($CHCl_3$, *c*. 0.5 g/100 mL); melting point = 121-124°C; ^{1}H NMR (500 MHz, CD_3OD) δ = 7.71-7.65 (1H, m), 7.41-7.35 (1H, m), 7.33-7.26 (2H, m), 4.83 (1H, d, J = 2.4 Hz), 4.71 (1H, d, J = 6.5 Hz), 4.69 (1H, d, J = 6.5 Hz), 4.48-4.27 (4H, m), 4.04 (1H, d, J = 9.7 Hz), 3.78 (1H, d, J = 9.7 Hz), 3.41 (3H, s), 3.11 (1H, dd, J = 8.1, 2.4 Hz, O**H**), 2.84-2.79 (2H, m), 2.29 (1H, dd, J = 6.9, 3.6 Hz, O**H**), 1.31 (3H, s), 0.67 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 135.9, 135.8, 127.1, 126.7, 126.6, 125.7, 110.9, 97.0, 86.5, 82.9, 71.3, 62.5, 60.0, 55.9, 42.5, 41.4, 27.8, 26.8; ν_{max} (film) 3317, 2985, 2930, 2899, 2863, 1483, 1339, 1281, 942 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{18}H_{26}O_6Na)^+$ 361.1622, found 361.1680.

Methyl (3a*R*,4*S*,9*R*,9a*S*,10*S*,11*R*)-10,11-dihydroxy-2,2-dimethyl-4,9-dihydro-4,9-ethanonaphtho[2,3-d][1,3]dioxole-9a(3aH)-carboxylate II-71

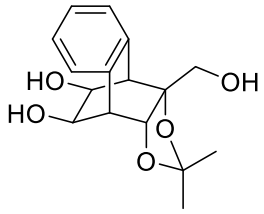


Alkene **II-61** (0.178 g, 0.622 mmol, 1.0 equiv.) was dissolved in acetone (8.0 mL) and NMO (0.109 g, 0.933 mmol, 1.5 equiv.) was added. Water (~0.5 mL) was added until full dissolution of NMO was

observed. To the resulting solution was added OsO_4 (2.5 wt% in *t*BuOH, 0.16 mL, 15.5 µmol, 2.5 mol%). The solution was heated to 65°C and stirred for 24 hours. After this time, the reaction was allowed to cool to RT and quenched through addition of aqueous sodium thiosulfate (20 mL). The product was extracted with EtOAc (3 x 20 mL). Combined aqueous phases were dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **II-71** as a colourless oil (0.158 g, 0.494 mmol, 79%).

R_f = 0.29 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = -23 (CH_2Cl_2, *c*. 1 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.32-7.22 (3H, m), 7.18-7.15 (1H, m), 4.82 (1H, d, J = 4.4 Hz), 4.67-4.55 (2H, m), 3.66 (1H, dd, J = 4.4, 3.1 Hz), 3.64 (1H, d, J = 2.6 Hz), 3.60 (3H, s), 2.10 (1H, d, J = 6.5 Hz, O**H**), 1.81 (1H, d, J = 6.8 Hz, O**H**), 1.55 (3H, s), 1.29 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 171.6, 135.2, 134.3, 128.5, 128.3, 128.2, 113.0, 85.0, 77.6, 64.9, 64.7, 52.8, 49.6, 47.0, 26.3, 24.9; ν_{max} (film) 3446, 2993, 2952, 1739, 1463, 1378, 1212, 1055, 1033 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{17}H_{20}O_6Na)^+$ 343.1152, found 343.1172.

(3a*R*,4*S*,9*R*,9a*R*,10*S*,11*R*)-9a-(Hydroxymethyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-ethanonaphtho[2,3-d][1,3]dioxole-10,11-diol II-72



Diol **II-71** (43 mg, 0.134 mmol, 1.0 equiv.) was dissolved in anhydrous THF (4.0 mL) and cooled to 0°C. $LiAlH_4$ (2.4 M, 0.11 mL, 0.264 mmol, 2.0 equiv.) was added dropwise and the solution allowed to warm to RT over 4 hours. The reaction was cooled to 0°C, quenched through slow addition of water (10 mL) and filtered. The product was extracted from the filtrate with EtOAc (3 x 10 mL) and the solvent removed to give **II-72** as a white solid (13 mg, 44.5 µmol, 33%), which was of suitable purity for full characterisation.

R_f = 0.43 (90% EtOAc, 10% petroleum ether); $[\alpha]_D^{25}$ = -13 (CH_2Cl_2, *c*. 0.5 g/100 mL); ^{1}H NMR (500 MHz, CD_3OD) δ = 7.29-7.19 (4H, m), 4.59 (1H, dd, J = 7.9, 3.2 Hz), 4.51 (1H, dd, J = 2.9, 2.8 Hz), 3.80 (1H, d, J = 4.4 Hz), 3.53 (1H, d, J = 2.8 Hz), 3.46 (1H, dd, J = 4.4, 3.2 Hz), 3.34 (1H, d, J = 11.9 Hz), 2.79 (1H, d, J = 11.9 Hz), 1.52 (3H, s), 1.42 (3H, s); ^{13}C NMR (126 MHz, CD_3OD) δ = 138.7, 136.6, 129.1, 128.9, 128.5, 128.2, 112.9, 87.6, 79.5, 67.4, 66.1, 65.9, 49.6, 27.6, 27.4; ν_{max} (film) 3355, 3260, 2962, 2933, 1405, 1376, 1210, 1034 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{16}H_{20}O_5Na)^+$ 315.1203, found 315.1233.

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32. All geometries were optimized using the M06-2X density functional the 6-31+G(d) basis set and an ultrafine integration grid within the IEFPCM solvent model (chloroform). Single point energies were calculated using M06-2X, the polarized, triple-ζ valence quality def2-TZVPP basis set and an ultrafine integration grid within the IEFPCM solvent model (chloroform). The resulting energies were used to correct the energies obtained from the M06-2X optimizations.
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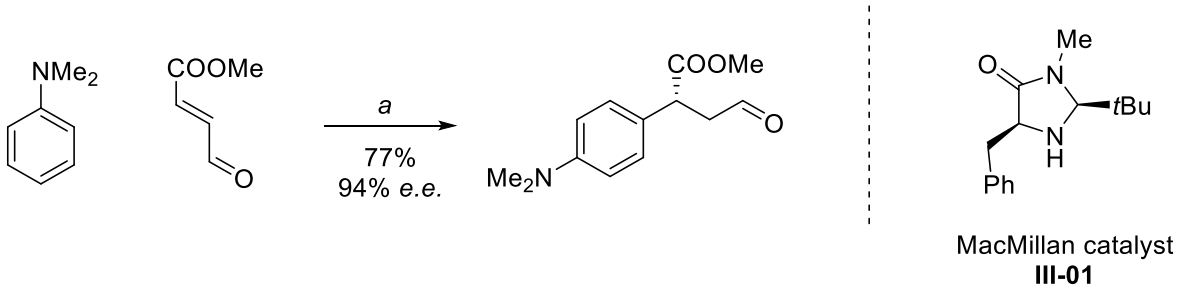
Synthesis and testing of a novel epoxidation catalyst

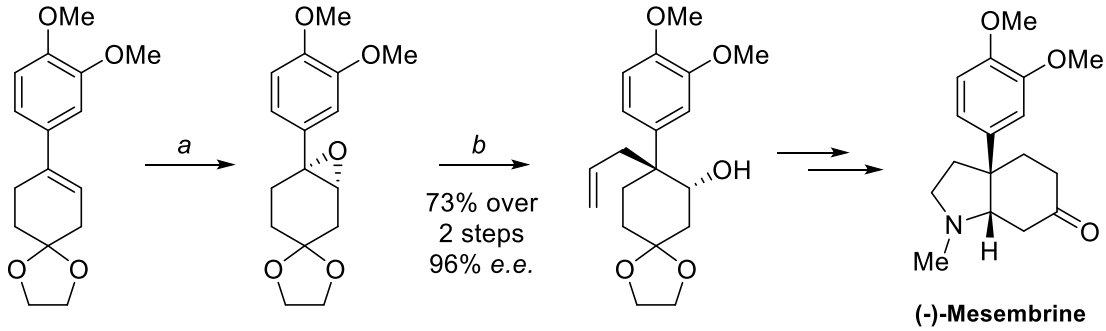
Introducing epoxidation catalysis

Over previous decades, numerous small organic molecules have been shown to be highly selective and efficient catalysts for a number of transformations.[1-3] In contrast to the majority of metal-based catalysts, organocatalysts also tend to be non-toxic, inexpensive and environmentally benign. These valuable features have led to significant interest in the synthesis of asymmetric organocatalysts. Some of the most well-known organocatalysts currently in use are so-called MacMillan catalysts, which are based on the imidazolidinone motif. MacMillan catalysts can be employed to catalyse a range of enantioselective transformations, including the fluorination of aldehydes,[4] intermolecular Michael additions[5] (scheme III-01) and Diels–Alder reactions.[6]



Scheme III-01: MacMillan catalyst **III-01** employed in a conjugate addition reaction.[5] *a*) **III-01**, $CHCl_3$, RT.

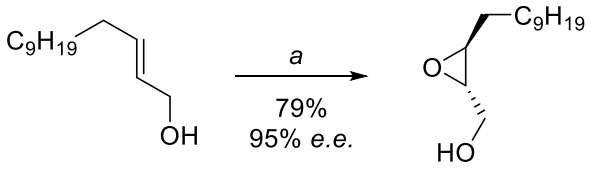
Asymmetric epoxidation catalysts enable the synthesis of enantiomerically pure epoxides from alkenes in one step.[7] The resulting epoxides may be further functionalised in a number of ways to furnish a variety of enantiopure compounds. As a result, epoxides can be used as key intermediates in the synthesis of biologically active compounds, for example (–)-Mesembrine[8] (scheme III-02), or as biologically active compounds themselves.[9, 10]



Scheme III-02: Epoxidation used in the total synthesis of (–)-Mesembrine.[8] *a*) Shi's epoxidation catalyst, Oxone®, DME, MeCN, water, 0°C. *b*) allylmagnesium chloride, THF, 0°C to RT.

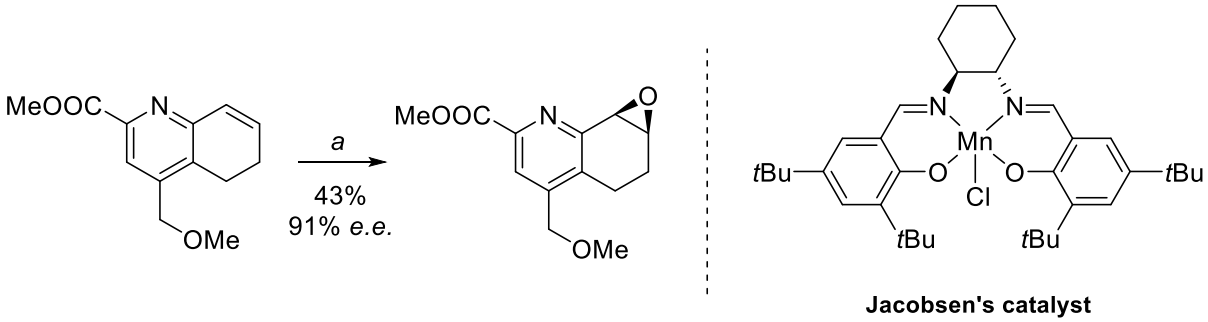
The value of epoxides has seen many asymmetric epoxidation catalysts developed over the previous decades. Two of the most popular metal-based methodologies for epoxide synthesis are the Sharpless

epoxidation[11] and epoxidation using Jacobsen's catalyst.[12, 13] The Sharpless epoxidation requires Ti(O*i*Pr)$_4$, TBHP and DET to enantioselectively epoxidize allylic alcohols (scheme III-03). Whilst this procedure does tend to provide epoxides with a high *e.e.*, the necessity of the substrate to be an allylic alcohol significantly reduces its utility.



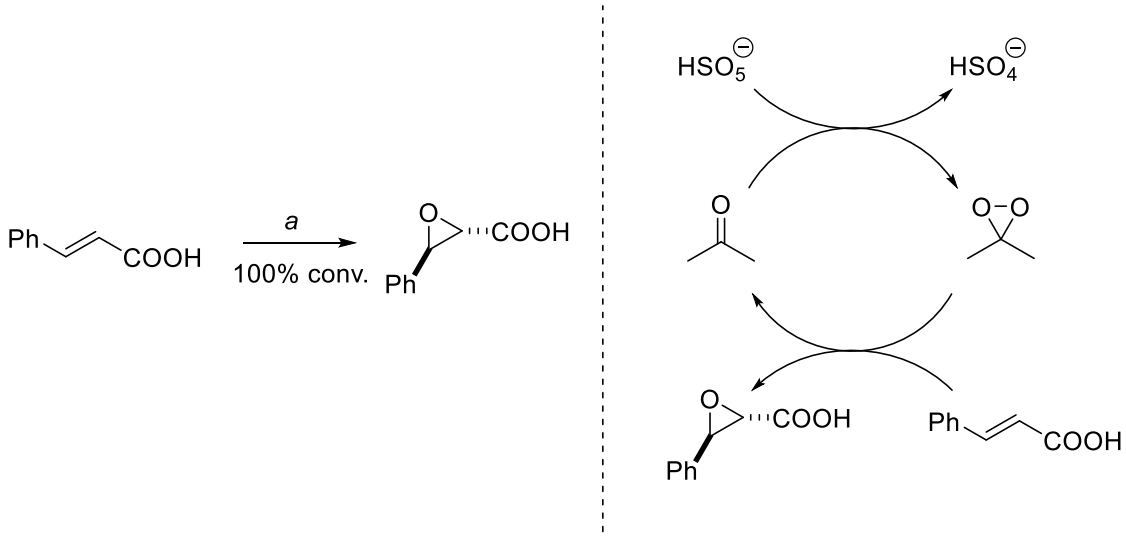
Scheme III-03: Example of an enantioselective Sharpless epoxidation.[11] *a*) L–(+)-DET, Ti(O*i*Pr)$_4$, butanoic acid, CH_2Cl_2, -20°C.

The Jacobsen (Katsuki) catalyst, independently developed in 1990 and 1991 by both Jacobsen and Katsuki,[12-14] utilises a manganese-salen complex to achieve the asymmetric epoxidation of olefins. Reported *e.e*.s using Jacobsen's catalyst tend to be high (90-95%), which has contributed, along with its ease of synthesis, to its wide-spread use. The utility of Jacobsen's catalyst is well illustrated by its use in Hashimoto's synthesis of the tetra-substituted dihydroquinoline fragment of Siomycin D$_1$ (scheme III-04) – a member of the thiostrepton family of peptide antibiotics.[15, 16]



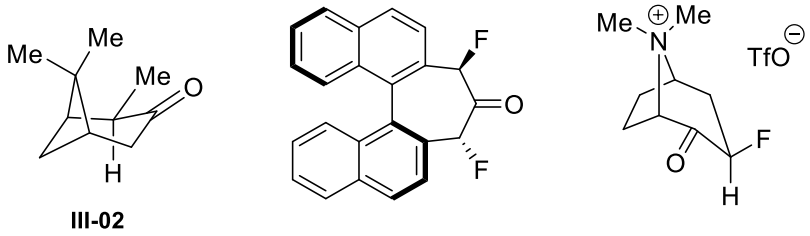
Scheme III-04: Epoxidation reaction used in the synthesis of a fragment of Siomycin D$_1$.[15] *a*) Jacobsen's catalyst, 4-phenylpyridine N-oxide, NaOCl, CH_2Cl_2, RT.

Due to the diminishing supply of transition metals and the toxicity generally associated with transition metal based complexes, the development of asymmetric epoxidation organocatalysts is highly desirable and has consequentially been pursued by several research groups.[2] In 1980, Curci reported the epoxidation of olefins using acetone and potassium peroxymonosulfate.[17] Upon reaction of acetone with potassium peroxymonosulfate, a reactive dioxirane is formed. Subsequent epoxidation of an olefin results in the dioxirane being converted back to its parent ketone (scheme III-05).



Scheme III-05: Conditions employed in the epoxidation of cinnamic acid using acetone and potassium peroxymonosulfate (left) and the catalytic cycle when epoxidizing cinnamic acid with acetone and potassium peroxymonosulfate (right).[17] *a*) potassium peroxymonosulfate, acetone, water, 2°C.

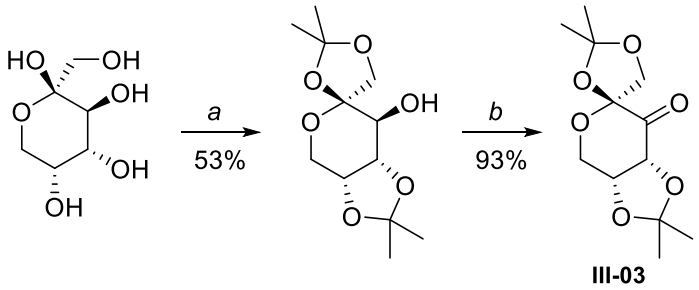
Curci later reported the first example of an enantiopure ketone being using in an epoxidation reaction in 1984.[18] Curci selected (+)-isopinocamphone **III-02** as the ketone in the epoxidation of *trans*-β-methylstyrene, which provided the corresponding epoxide with an *e.e.* of 11-12%. Subsequently, several other ketones have been tested as enantioselective epoxidation organocatalysts,[2] including binaphthyl based α-fluoroketones[19] and ammonium α-fluoroketones[20] (figure III-01).



III-02

Figure III-01: Examples of ketones tested as asymmetric epoxidation catalysts.[18, 19]

Research into the use of carbohydrate-derived ketones as asymmetric epoxidation catalysts has been pioneered by Shi. Shi first reported the use of D-fructose derived ketone **III-03** in asymmetric epoxidation reactions in 1996.[21] Three key principles governed Shi's catalyst design: close proximity between the stereogenic centres and the reactive centre (ketone); a spiro-acetonide group to minimise ring-flipping between chair conformations; an acetonide group on alcohols C2 and C3 to act as a face blocking group.



Scheme III-06: Synthesis of Shi's catalyst from D-fructose.[21] *a*) $HClO_4$, acetone, 0°C. *b*) PCC, CH_2Cl_2, RT.

Shi catalyst **III-03** can be easily synthesised in 2 steps from fructose (scheme III-06).[21] Its ease of synthesis has been essential in ensuring its success as an epoxidation catalyst, with applications in the total syntheses of Cryptophycin 52 and (+)-Murisolin.[22, 23] Its popularity is further enhanced by a vast substrate scope (figure III-02). One of the major limitations of Shi's catalyst, however, is the high catalyst loadings required as a result of catalyst de-activation through Baeyer–Villiger rearrangement, which occurs at low pH.[24] Catalyst de-activation can be somewhat mitigated by careful control of the reaction pH, however catalyst loadings of 20-30 mol% are generally still required.

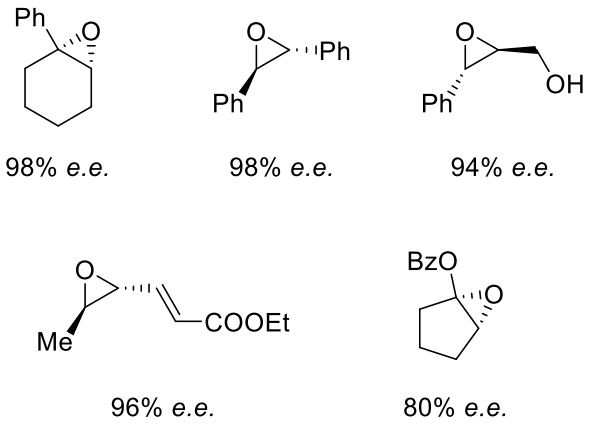
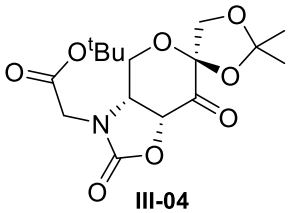


Figure III-02: A selection of epoxides synthesised using Shi's catalyst.[24]

Shi has investigated a wide range of carbohydrate-based ketones for asymmetric epoxidation reactions since the discovery of Shi's original catalyst **III-03**.[2] Some of these ketones have proved less prone to de-activation at low pH. The most notable of these is perhaps the oxazolidinone containing catalyst (**III-04**, figure III-03), which requires a catalyst loading of ≤5 mol%.[25] Shi proposed that, due to the migratory aptitude of substituents in Baeyer–Villiger reactions being influenced by electronic factors, increasing the electron deficiency at the α carbon would result in in Baeyer–Villiger rearrangement of the catalyst being disfavoured. Despite ketone **III-04** also epoxidizing a range of olefins with high *e.e.*, the number of synthetic steps required to synthesise it from D-fructose precludes its widespread use in synthesis.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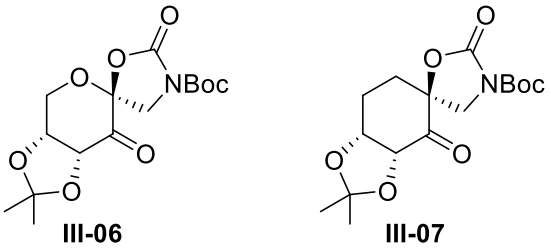


Figure III-05: Structures oxazolidinone containing catalysts synthesised by Shi.[27]

Shi examined the possible transition states in the formation of styrene oxides using both catalysts **III-06** and **III-07** and drew conclusions based on this. Through analysis of both catalysts in the epoxidation of a range of olefins, Shi proposed that the removal of the pyranose oxygen of **III-06** to form carbocyclic **III-07** resulted in the *spiro* transition state being favoured to a greater extent than in the case of *o*-heterocyclic **III-06**, resulting in carbocyclic ketone **III-07** epoxidizing styrene with greater enantioselectivity (figure III-06).[27] Shi's comprehensive work in this regard demonstrates the potential utility of carbocyclic ketones as asymmetric epoxidation catalysis.

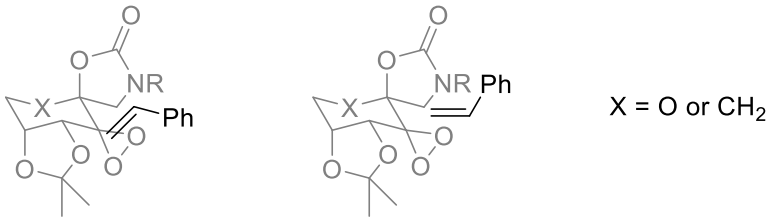
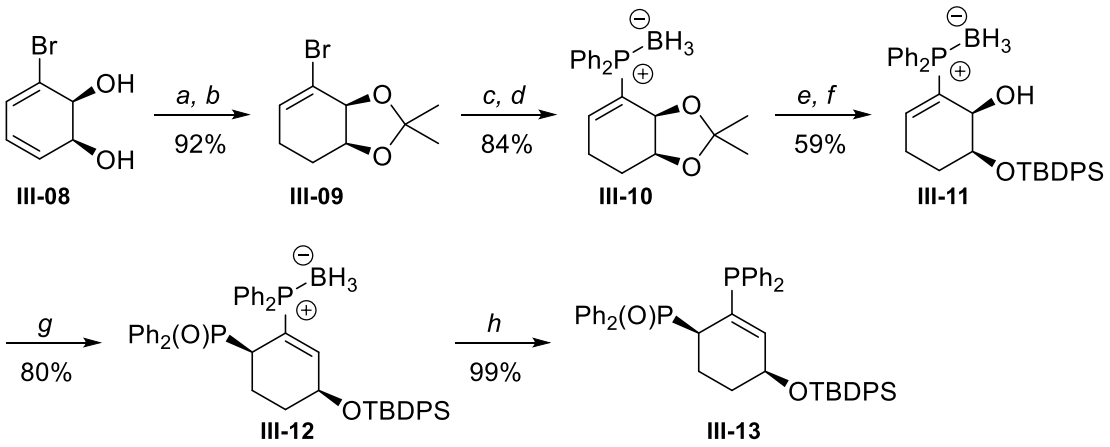


Figure III-06: Spiro-transition state preferentially adopted when using **III-06** and **III-07** in the epoxidation of styrene (left) compared to the less favoured planar transition state (right).[27]

Organocatalysts derived from arene diols

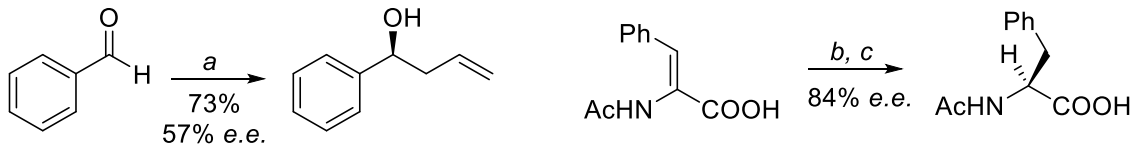
Arene dioxygenases allow the environmentally benign synthesis of enantiopure arene *cis*-diols from simple aromatics.[28] Such aromatics tend to be both abundant and inexpensive, making the bulk synthesis of asymmetric organocatalysts from arene *cis*-diol is desirable. Whilst arene diols have shown utility in the synthesis of numerous natural products and compounds of biological interest,[29-33] their use in the synthesis of organocatalysts has only been reported on a single occasion.

In 2011, Stevenson, Boyd and co-workers reported the synthesis of a phosphine–phosphine oxide catalyst from bromo-benzene (scheme III-07).[34] Following the microbial oxidation of bromo-benzene to bromo-arene diol **III-08** using *Pseudomonas putida* UV4, hydrogenation and acetonide protection gave bromo-alkene **III-09**. A palladium catalysed coupling reaction was then employed to install the first phosphorous group, which was subsequently reacted with borane to furnish ylide **III-10**. After converting acetonide protected **III-10** to TBDPS protected **III-11**, phosphination of the alcohol with chloro-diphenylphosphine resulted in immediate Arbuzov [2,3]-rearrangement to give phosphine oxide **III-12**, which was then converted to the phosphine-phosphine oxide **III-13**.



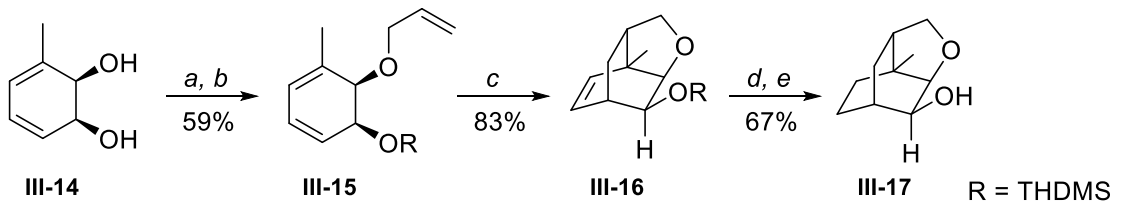
Scheme III-07: Synthesis of phosphine–phosphine oxide **III-13** as reported by Stevenson and Boyd.[34] *a*) Rh/graphite, H_2, MeOH. *b*) *p*TSA, 2,2-DMP, acetone. *c*) $HPPh_2$, $Pd(OAc)_2$, Cs_2CO_3, DPPF, toluene. *d*) BH_3.THF. *e*) TFA, THF, water. *f*) TBDPSCl, imidazole, DMF. *g*) $ClPPh_2$, DMAP, THF. *h*) Et_2NH.

III-13 was subsequently tested as an asymmetric organocatalyst in the allylation of aromatic aldehydes and as a chiral ligand in the hydrogenation of several olefins.[34] Aromatic aldehydes were successfully allylated using allyltrimethylsilane and catalytic **III-13**, with benzaldehyde being converted in the highest *e.e.* of all tested substrates (scheme III-08). In general, hydrogenation reactions of olefins using $[Rh(cod)Cl]_2$ and **III-13** as a chiral ligand proceeded with low enantioselectivity, however a standout result was seen in the hydrogenation of α-acetamidocinnamic acid. Whilst the reported *e.e.*s of products obtained from **III-13** catalysed allylation and hydrogenation reactions tend to be modest. Boyd has also previously reported the synthesis of an arene diol derived ligand that has been tested in metal catalysed asymmetric allylic oxidation and in the cyclopropanation of alkenes.[35]



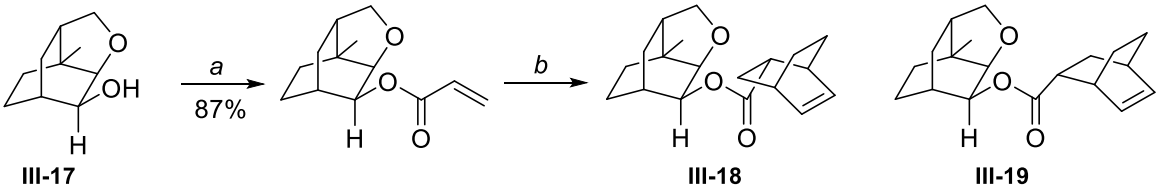
Scheme III-08: Allylation of benzaldehyde catalysed by **III-13**.[34] *a*) **III-13** (15 mol%), allyltrimethylsilane, DIPEA, CH_2Cl_2. *b*) $[Rh(cod)Cl]_2$ (1 mol%), **III-13** (2 mol%), MeOH, EtOH, $NaBF_4$. *c*) H_2, MeOH.

In addition to Boyd's research in this field, Hudlický has also contributed through the synthesis of chiral auxiliary **III-17** from arene diol **III-14** (scheme III-09).[36] The key step in the synthesis of chiral auxiliary **III-14** is the intramolecular Diels–Alder reaction of **III-15** to form poly-cyclic **III-16**.



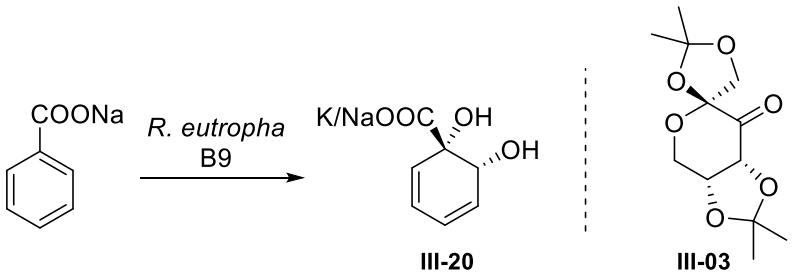
Scheme III-09: Hudlický's synthesis of chiral auxiliary **III-17**.[36] *a*) THDMSCl, imidazole, DMF. *b*) allyl bromide, NaH, THF. *c*) THF, reflux. *d*) Pd/C, H_2, EtOH. *e*) TBAF, THF.

III-17 has been used as a chiral auxiliary in an intermolecular Diels–Alder reaction, furnishing **III-18** and **III-19** (scheme III-10).[36] Reductive cleavage of esters **III-18** and **III-19** gave alcohols which were shown to be entirely racemic. Hudlický additionally reported the synthesis of a oxaziridine from **III-17** which was used in the α-hydroxylation of 2-phenylacetophenone, furnished a product with an *e.e.* of just 16%. Whilst the research of Hudlický and Boyd has thus far yielded asymmetric catalysts and chiral auxiliaries which are, in certain cases, marginally enantioselective, the modest *e.e.*s obtained do suggest that structural changes can be made to obtain more efficient catalysts from arene *ortho,meta*-diols.



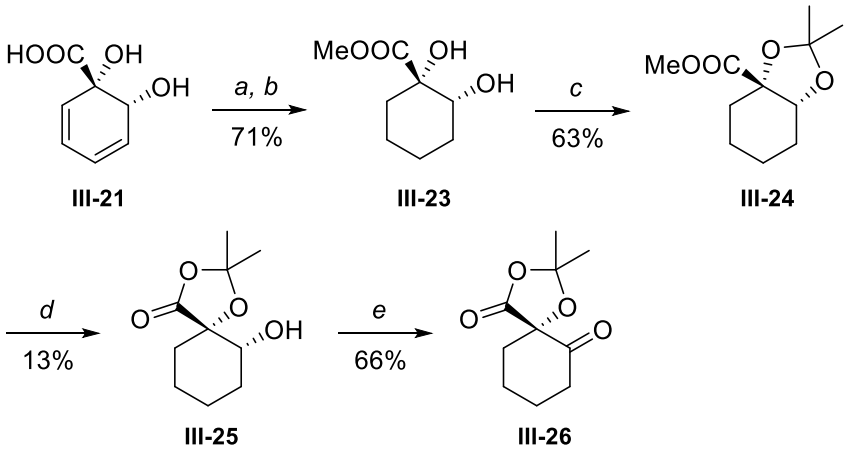
Scheme III-10: Diels–Alder reaction using **III-17** as a chiral auxiliary. *a*) Acryloyl chloride, NEt_3, THF. *b*) cyclohexadiene, toluene.

The microbial dihydroxylation of sodium benzoate was first reported by Reiner in 1971, resulting in the formation of arene diol **III-20** (scheme III-11).[37] Upon examination of arene diol **III-20**, structural similarities between it and Shi's catalyst **III-03** can be easily identified. Both compounds possess an enantiopure tetra-substituted carbon adjacent to a carbon bearing an oxygen atom. Due to this similarity, Lewis *et al*. believed arene *ipso,ortho*-diol **III-20** could be a precursor to a microbially derived epoxidation catalyst.[38]



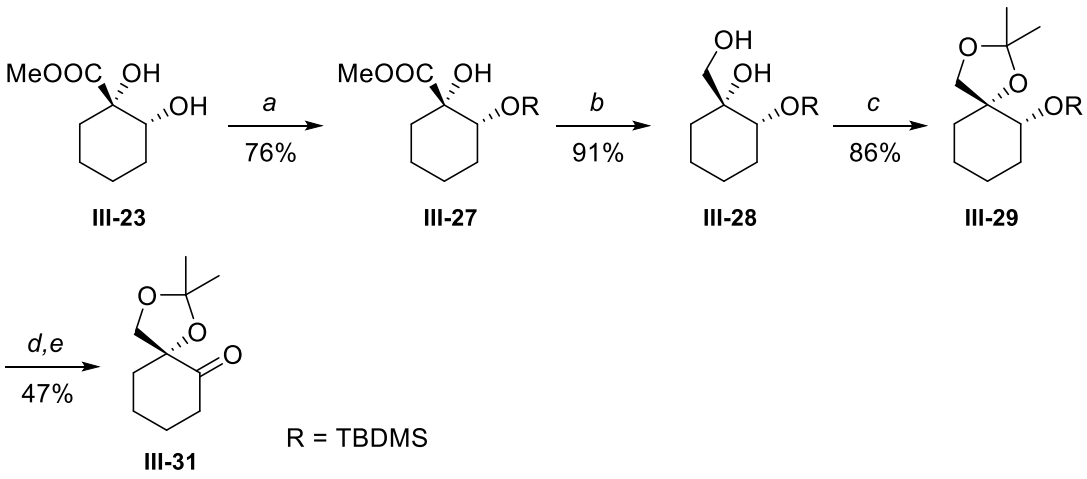
Scheme III-11: Microbial de-aromative oxidation of sodium benzoate (left) and Shi's catalyst **III-03** (right).[21, 37]

Lewis *et al.* synthesised two carbocyclic Shi-like epoxidation catalysts for testing from arene diol **III-21** (scheme III-12).[39] Alcohol **III-25** was synthesised serendipitously through reacting methyl ester **III-24**, a derivative of arene diol **III-21**, with NaOH. This transformation was caused by base mediated hydrolysis of the methyl ester and subsequent isomerisation of the acetonide. Oxidation of alcohol **III-25** with Dess–Martin periodinane then furnished ketone **III-26**.



Scheme III-12: Synthesis of ketone **III-26** from arene diol **III-21**.[39] *a*) Pd/C, H_2, MeOH, RT. *b*) TMS-CHN_2, MeOH, benzene, RT. *c*) *p*TSA, 2,2-DMP, acetone, RT. *d*) NaOH, water, THF, RT. *e*) DMP, CH_2Cl_2, 0°C to RT.

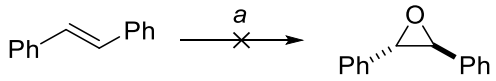
Ketone **III-31** was also synthesised by Lewis and co-workers. [39] After protection of the secondary alcohol of diol **III-23** as its TBDMS ether, reduction of methyl ester **III-27** was conducted, furnishing diol **III-28**. Reacting diol **III-28** with catalytic acid in 2,2-DMP and acetone resulted in formation of spiro-cyclic acetonide **III-29**. Deprotection of the TBDMS group and oxidation of the unmasked secondary alcohol then gave target ketone **III-31**. Overall, the synthesis of ketone **III-31** was achieved in a 20% yield over 7 steps from arene diol **III-21** (scheme III-13).



Scheme III-13: Synthesis of ketone **III-31** from diol **III-23**.[39] *a*) TBDMSOTf, NEt_3, CH_2Cl_2, -78°C to RT. *b*) $LiBH_4$, THF, -78°C to RT. *c*) *p*TSA, 2,2-DMP, acetone, RT. *d*) TBAF, THF, 0°C to RT. *e*) DMP, CH_2Cl_2, 0°C to RT.

In the evaluation of ketones **III-26** and **III-31** as epoxidation catalysts, Lewis and co-workers chose *trans*-stilbene as a test substrate.[38] *Trans*-stilbene has been shown to be epoxidized in good yields and with a high *e.e.* when using Shi's catalyst, so conditions identical to those used by Shi were employed when instead using ketones **III-26** and **III-31** as epoxidation catalysts. Lewis and co-workers found that ketones **III-26** and **III-31** both failed as epoxidation catalysts under these conditions (scheme III-14). Based on this observation, and those made by Shi in the testing of carbocyclic epoxidation catalysts,

Lewis concluded that both the pyranose oxygen and the C2 and C3 bound oxygens of Shi's catalyst **III-03** are necessary to activate the ketone to electrophilic attack from peroxymonosulfate (Oxone®).



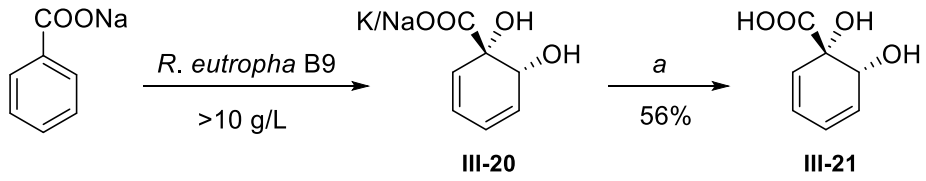
Scheme III-14: Attempted epoxidation of *trans*-stilbene using **III-31**. *a*) Oxone®, K_2CO_3, **III-31**, MeCN, water, 0°C.

In continuation of this initial research, the synthesis of an arene diol-derived ketone that is more prone to electrophilic attack from peroxymonosulfate (Oxone®) was pursued. This was to be achieved through the incorporation of an electron-withdrawing group onto the carbocyclic scaffold. It was hoped that such a compound may possess catalytic activity that is complementary to current methods for asymmetric epoxidation reactions.

Results and discussion

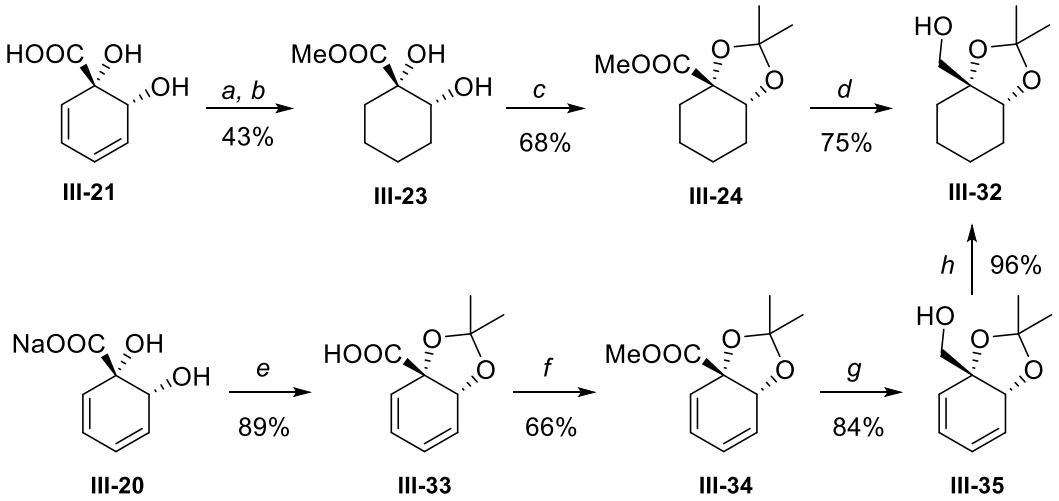
Following Reiner's seminal paper on the microbial oxidation of sodium benzoate to arene diol **III-20**,[37] iterative improvements to the biotransformation procedure have been made by several research groups.[40-42] The procedure adopted in our research bears a high similarity to the most successful reported procedures. Arene diol **III-20** was thus synthesised from sodium benzoate using *Ralstonia eutropha* B9 (scheme III-15).

Carboxylate **III-20** can be easily accessed from the concentrated supernatant of the biotransformation by affecting its precipitation as a mixed Na/K salt from addition of isopropanol, which was first demonstrated by Mihovilovic.[41] Acid **III-21** may be subsequently accessed through acidification of carboxylate **III-20** (scheme III-15). Acidifying carboxylate **III-20**, however, results in partial acid catalysed re-aromatisation of the arene diol, resulting in loss of valuable starting material. As such, it is desirable to utilise synthetic methodology which can be performed on carboxylate **III-20** in the synthesis of arene diol derivatives.



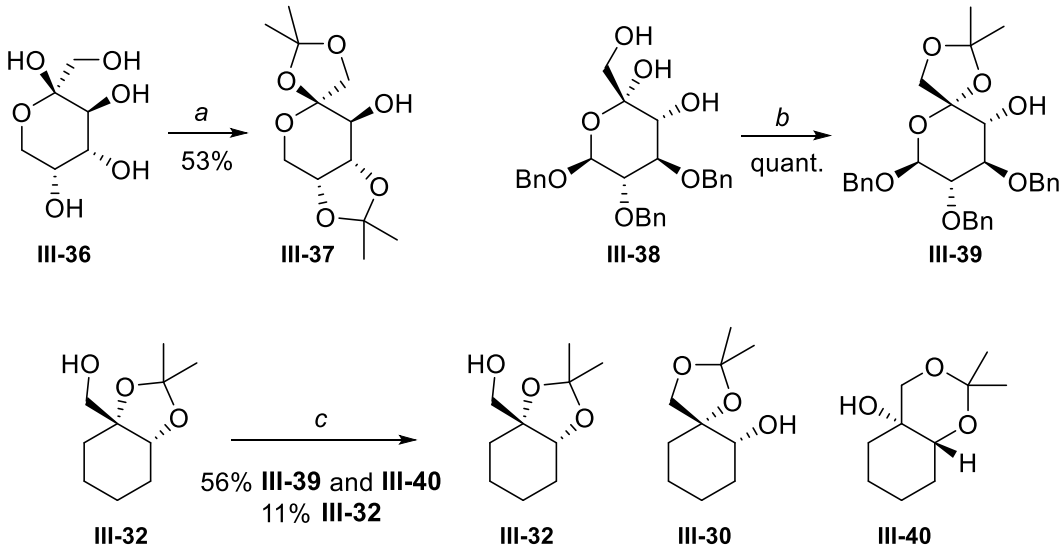
Scheme III-15: Microbial oxidation of sodium benzoate to afford carboxylate **III-20** and acid **III-21**. *a*) conc. HCl, water, 0°C.

At the outset of this project, it was supposed that developing conditions under which acetonide isomerisation may occur could be of utility. Being able to synthesise non-spiro-cyclic acetonides and readily convert them to their spiro-cyclic regio-isomers could reduce the number of steps required to synthesise an epoxidation catalyst, as well as allowing its synthesis to start from carboxylate **III-20**. To this end, alcohol **III-32** was synthesised as a substrate upon which to test acetonide isomerisation conditions (scheme III-16). The synthesis of alcohol **III-32** was achieved from both acid diol **III-21** and carboxylate **III-20**. Conditions developed using carboxylate **III-20** as a starting material gave alcohol **III-32** in the greater overall yield (47% over 4 steps).



Scheme III-16: Synthesis of primary alcohol **III-32**. *a*) Pd/C, H_2, MeOH, RT, 23 hours. *b*) TMS-CHN_2, MeOH, benzene, RT, 20 minutes. *c*) *p*TSA, 2,2-DMP, acetone, RT, 18 hours. *d*) $LiBH_4$ (2.0 equiv.), THF, -78°C to RT, 18 hours. *e*) TFA (5.0 equiv.), 2,2-DMP, 0°C to RT, 24 hours. *f*) TMS-CHN_2, MeOH, benzene, RT, 20 minutes. *g*) $LiBH_4$ (2 equiv.), THF, 0°C to RT, 16 hours. *h*) Pd/C, H_2, MeOH, RT, 4 hours.

In the first step of the synthesis of Shi's catalyst (scheme III-17), penta-ol **III-36** is subjected to acetonide protection conditions resulting in preferential formation of spiro-acetonide **III-37**.[21] In addition to this, Thiem reported exclusive spiro-cyclic acetonide formation when subjecting triol **III-38** to similar acetonide protection conditions, giving **III-39**.[43] Accordingly, it was envisaged that an acetonide isomerisation reaction on alcohol **III-32** would result in spiro-cyclic **III-30** being formed as the major product. Reacting **III-32** with *p*TSA in MeCN, acetone and 2,2-dimethoxypropane was found to furnish 2 new products in addition to the starting material (scheme III-17).



Scheme III-17: Acid catalysed acetonide group migration of alcohol **III-32**. *a*) $HClO_4$, acetone, 0°C.[21] *b*) DOWEX 50W, 2,2-DMP, acetone, RT.[43] *c*) *p*TSA (1 mol%), MeCN, acetone, 2,2-DMP, RT, 75 minutes.

Starting material **III-32** was isolable from the mixture through column chromatography, however the remaining 2 compounds synthesised from the isomerisation reaction were inseparable by column chromatography. Through comparison of the ^{1}H NMR spectrum of the mixture of these compounds (figure III-07) with the ^{1}H NMR spectrum of pure **III-30** previously reported by Lewis *et al.*,[39] spirocyclic **III-30** was found to be the major constituent of the mixture. Mass spectrometry suggested that spirocyclic acetonide **III-30** and the remaining unidentified component of the mixture are isomeric. Thus, the identity of this remaining component has been tentatively assigned as **III-40** based on this observation and further examination of the 1D and 2D NMR spectra of the mixture. AB protons H^{10} for minor product **III-40** manifest themselves as doublet δ = 3.46 and doublet δ = 3.72, which overlaps with a doublet of the major regio-isomer **III-30**. Methine proton H^{12} of minor product **III-40** manifests itself as dd δ = 3.68, whereas doublet δ = 2.94 is thought to be a result of the hydroxyl proton H^{11}, which seemingly shows long range coupling to another proton. These observations are supported by analysis of the HSQC spectrum of the mixture.

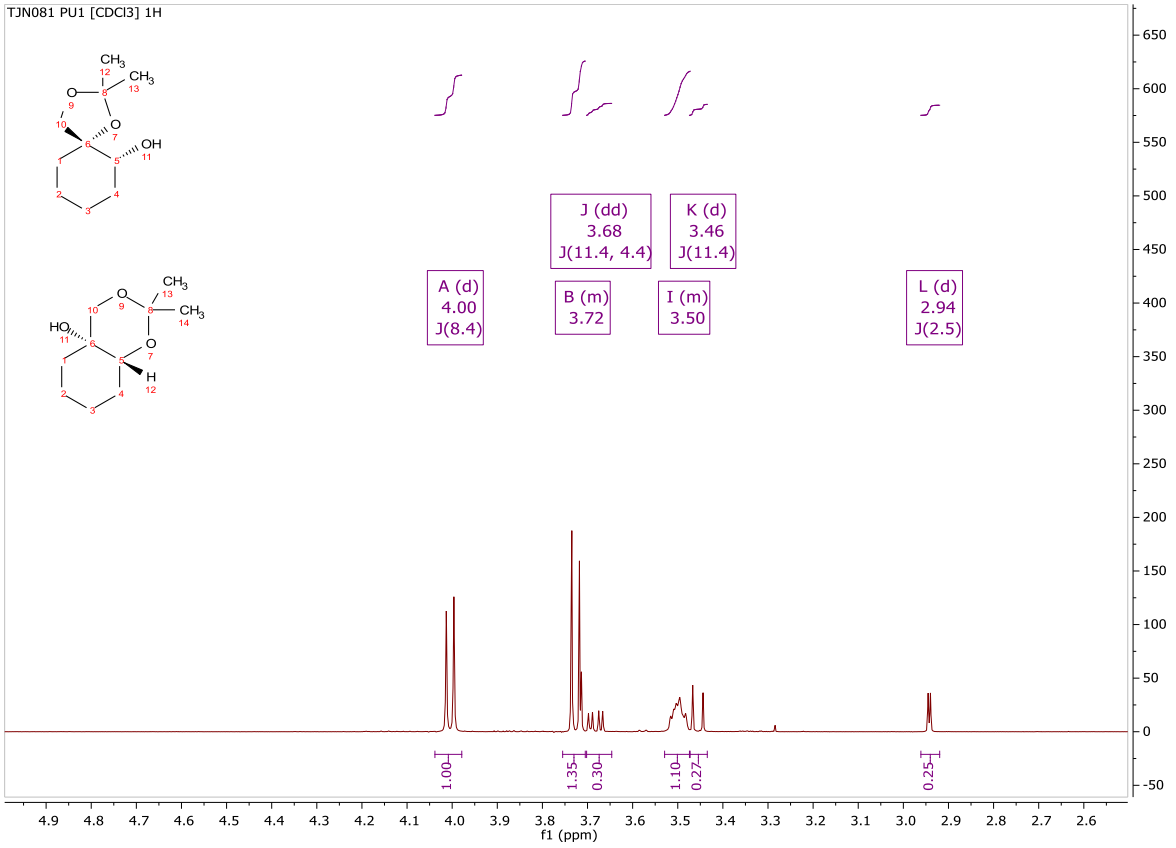
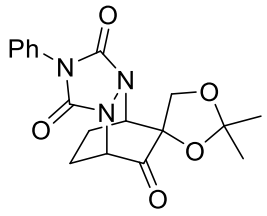


Figure III-07: ^{1}H NMR spectrum of inseparable regio-isomers **III-30** and **III-40**.

The presence of minor product **III-40** was deemed unproblematic in achieving the synthesis of a ketone catalyst from arene diol **III-30**. It was envisaged that, should similar products be formed when conducting this isomerisation reaction on more highly functionalised acetonides, the subsequent oxidation reaction to form a ketone would affect only the secondary alcohol **III-30** whilst the tertiary

alcohol of **III-40** would remain un-changed. The difference in polarity between the resulting molecules would then be such that one would predict they would be separable by column chromatography.

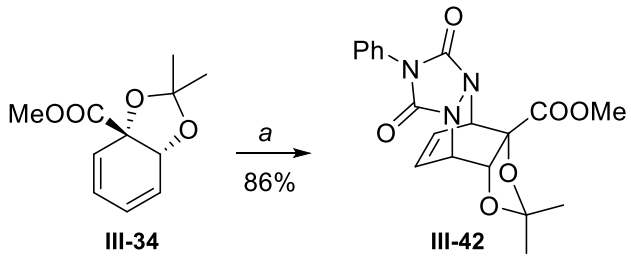
With isomerisation conditions developed for the synthesis of spiro-acetonide **III-32**, attention was turned to incorporating functionality onto the carbocyclic scaffold of arene diol **III-20** which would confer an increase to the rings electrophilicity and rigidity. In 1995, Widdowson reported the cycloaddition of PTAD with arene diol derivatives.[44] It was thought that the incorporation of a PTAD group may not only increase the electrophilicity of the ketone, but also act as a steric blocking group, inhibiting substrate approach from its face. Ketone **III-41a** was therefore targeted for synthesis and testing as an epoxidation catalyst (figure III-08).



III-41a

Figure III-08: Target epoxidation catalyst **III-41a**.

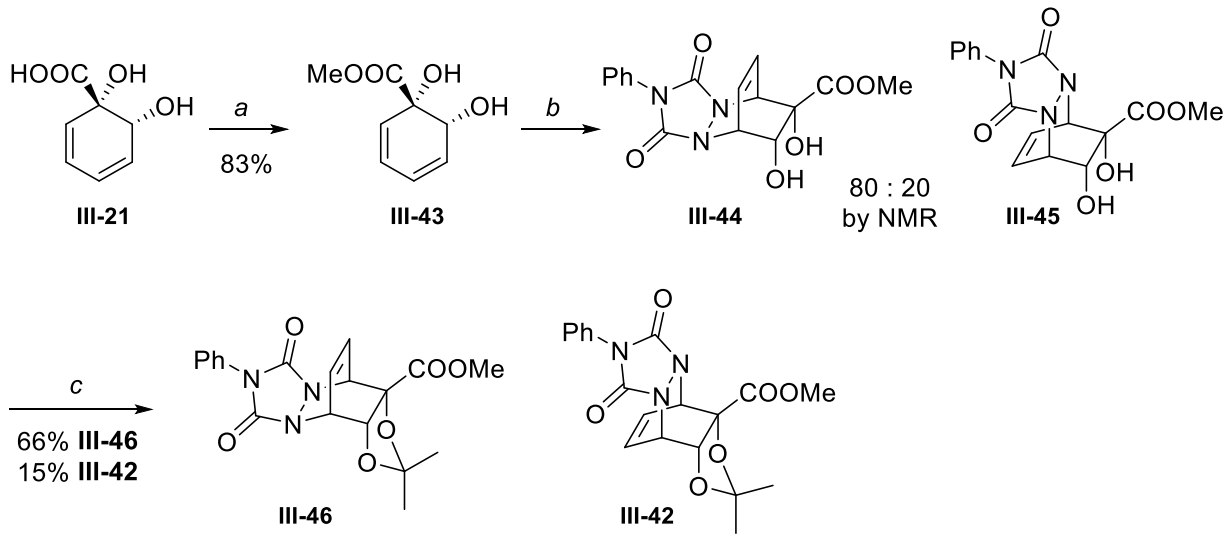
The cycloaddition of PTAD with dienes **III-34** and **III-43** proceeded as reported by Widdowson.[44] The cyclo-addition reaction between acetonide protected **III-34** and PTAD proceeded in an entirely diastereoselective fashion, affording cycloadduct **III-42** in a very good yield (scheme III-18). This selectivity can be rationalised based on the steric blocking effect exerted by the acetonide group.



III-34 **III-42**

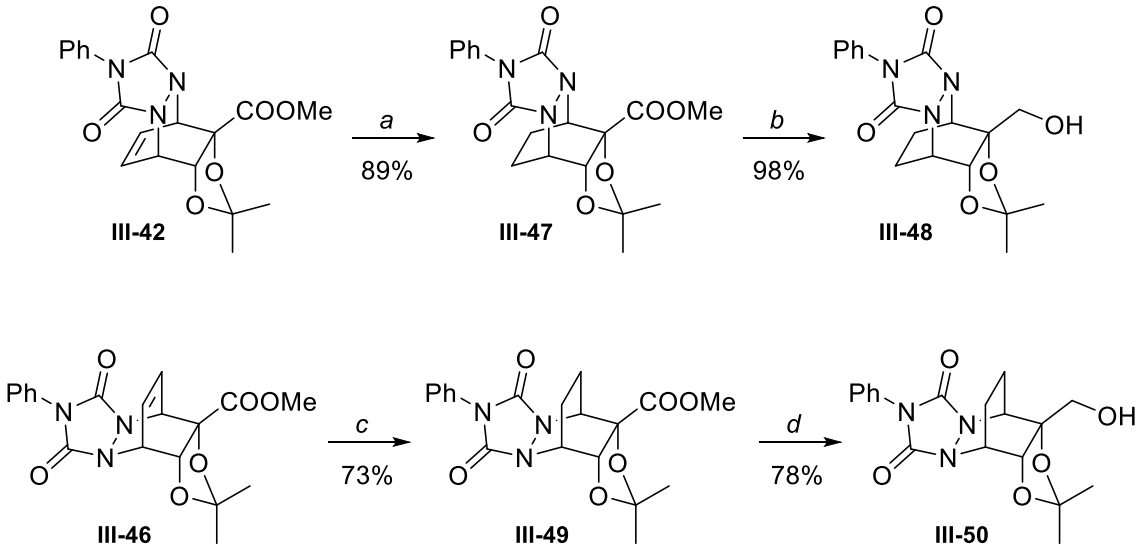
Scheme III-18: Diels–Alder reaction of PTAD with dienes **III-34**. *a*) PTAD (1.0 equiv.), acetone, RT, 90 minutes.

Also consistent with Widdowson's findings, upon reaction of PTAD with diol **III-43** (scheme III-19), a mixture of inseparable diastereomers **III-44** and **III-45** was obtained in a 80 : 20 ratio (as determined by ^{1}H NMR of the mixture).[44] Two factors may contribute to the observed diastereoselectivity of this reaction. Firstly, a steric clash between the methyl ester of diene **III-43** and the incoming PTAD group may disfavour addition of PTAD to the *top* face of the diene. Secondly, hydrogen bonding interactions between the hydroxyl groups and PTAD may direct addition of PTAD to the *bottom* face of diene **III-43**. Subsequent protection of diols **III-44** and **III-45** as their acetonides gave diastereomers **III-46** and **III-42**, which were separable by column chromatography (scheme III-19).[44]



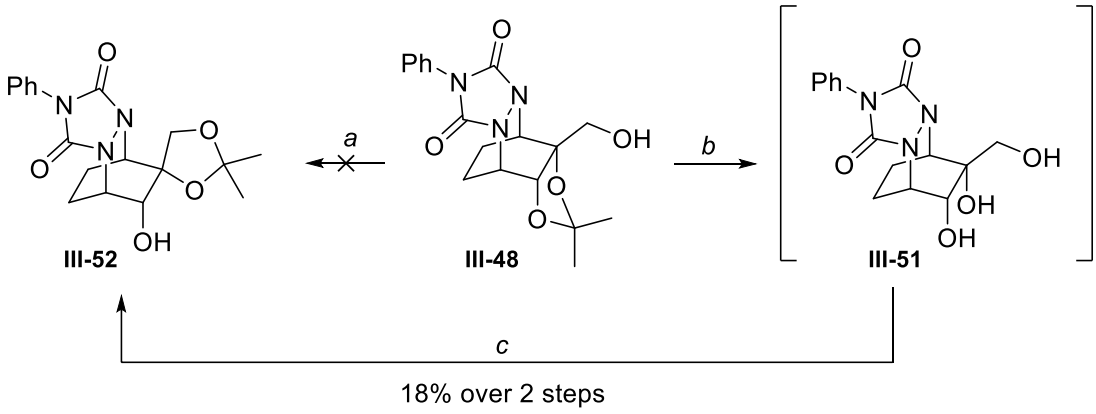
Scheme III-19: Cycloaddition of diene **III-43** and PTAD, with acetonide protection of the resulting diastereomers. *a*) $TMSCHN_2$, MeOH, benzene, RT. *b*) PTAD (1.0 equiv.), acetone, RT, 90 minutes. *c*) *p*TSA (5 mol%), 2,2-DMP, acetone, RT, 20 hours.

With pure diastereomers **III-42** and **III-46** in hand, synthetic transformations were conducted to furnish primary alcohols **III-48** and **III-50** (scheme III-20). The synthesis of **III-48** was achieved first through hydrogenation of alkene **III-42** using Pd/C and hydrogen gas, followed by $LiBH_4$ mediated reduction of the methyl ester **III-47**. Similar experimental conditions were used in the synthesis of alcohol **III-50**. Both these compounds were valid candidates upon which to attempt an acetonide isomerisation reaction.



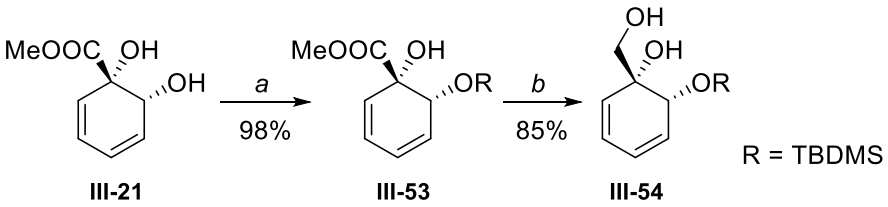
Scheme III-20: Synthesis of diastereomeric alcohols **III-48** and **III-50**. *a*) H_2, Pd/C, MeOH, RT, 72 hours. *b*) $LiBH_4$ (3.6 equiv.), THF, 0°C to RT, 4 days. *c*) H_2, Pd/C, MeOH, RT, 16 hours. *d*) $LiBH_4$ (6.5 equiv.), THF, 0°C to RT, 3 days.

When attempting the acetonide isomerisation conditions developed previously on alcohol **III-48**, no reaction was observed (scheme III-21). To the contrary, the acetonide of alcohol **III-48** proved significantly more stable than that of test substrate **III-32**. Stirring acetonide **III-48** in acid (AcOH, 37% HCl, DOWEX 50W-X8, 20-50 mesh) and MeOH and/or water at room temperature produced no reaction. Iodine mediated deprotection of the acetonide in MeOH also failed. In order to deprotect acetonide **III-48**, it was necessary to heat a solution of **III-48** in MeOH and conc. HCl to reflux for several hours (scheme III-21). After removing the solvent under vacuum, formation of triol **III-51** was confirmed by crude ^{1}H NMR. This material was immediately subjected to acetonide protection conditions, giving spirocyclic acetonide **III-52** exclusively, albeit in a low yield. The low yield for this reaction may be a consequence of the harsh conditions used in the deprotection step, resulting in starting material or product degradation.



Scheme III-21: Synthesis of spiro-cyclic acetonide **III-52**. *a*) *p*TSA (1 mol%), MeCN, 2,2-DMP, acetone, RT, 24 hours. *b*) HCl (conc.), MeOH, reflux, 2 hours. *c*) *p*TSA (5 mol%), 2,2-DMP, RT, 16 hours.

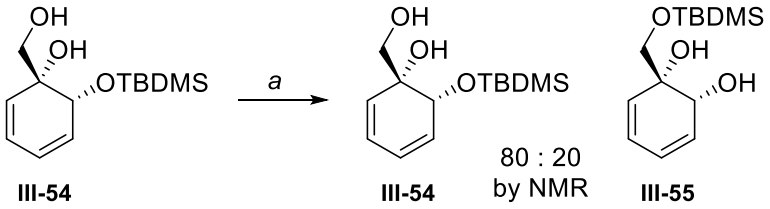
Due to the low yielding synthesis of acetonide **III-52**, an alternative route to target ketone **III-41** was devised. The revised method relied upon a TBDMS protected secondary alcohol sterically inhibiting approach of PTAD to the *bottom* face of the diene. As such, diene **III-54** was synthesised in 2 steps from methyl ester **III-21**, with the aim of using this diene in the synthesis of **III-41a** (scheme III-22).



Scheme III-22: Synthesis of diene **III-54**. *a*) TBDMSOTf (1.05 equiv.), NEt_3 (1.2 equiv.), CH_2Cl_2, -78^{o}C to RT, 5 hours. *b*) $LiBH_4$ (2.0 equiv.), THF, 0^{o}C to RT, 16 hours.

Despite diol **III-54** being successfully synthesised, upon purification of the crude material by column chromatography an undesired side product was observed to form (scheme III-23). It is believed that

this side product is a regioisomer of diol **III-54** which arises due to TBDMS migration to the primary alcohol. Mass spectrometry confirms that both components of the mixture have the same molecular mass, which helps to confirm this proposition. Furthermore, the ^{1}H NMR spectrum of the mixture indicates that both compounds possess the same functional groups (figure III-09). 4 alkene protons can be observed for each isomer in the region δ = 6.25-5.50. The AB protons for the major product **III-54** can be seen as doublets δ = 3.52 and δ = 3.42, whilst the AB protons for the minor product **III-55** manifest themselves as doublets δ = 3.73 and δ = 3.62. Methine protons H^{5} for both products overlap to form doublet δ = 4.35. TBDMS proton peaks are also present for both isomers.



Scheme III-23: Proposed silica catalysed migration of TBDMS. *a*) column chromatography on SiO_2 at RT.

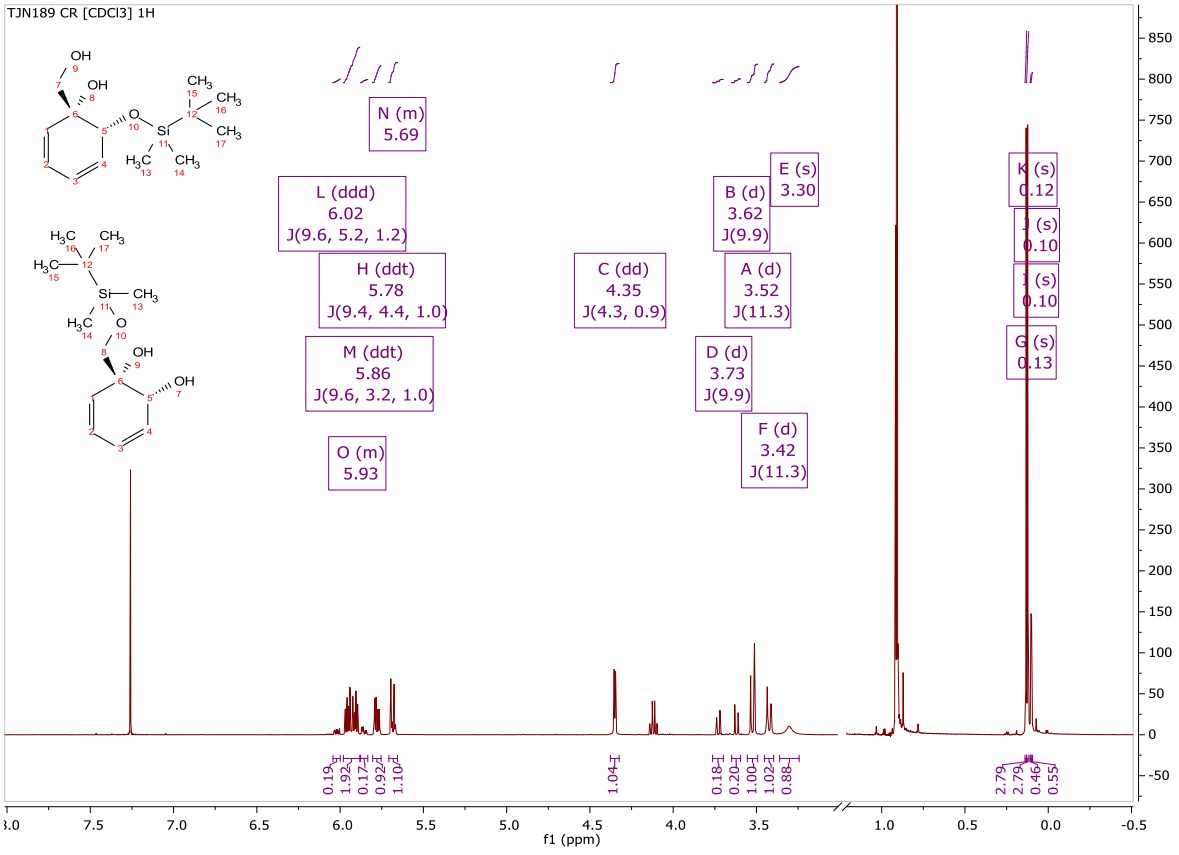
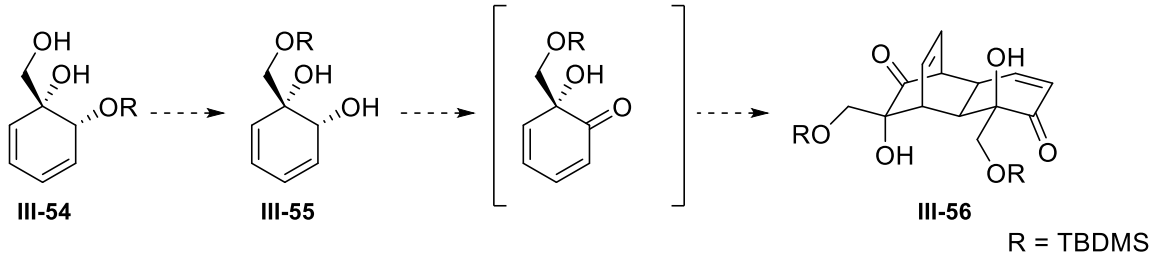


Figure III-09: ^{1}H NMR spectrum of diol **III-54** and its regioisomer **III-55**.

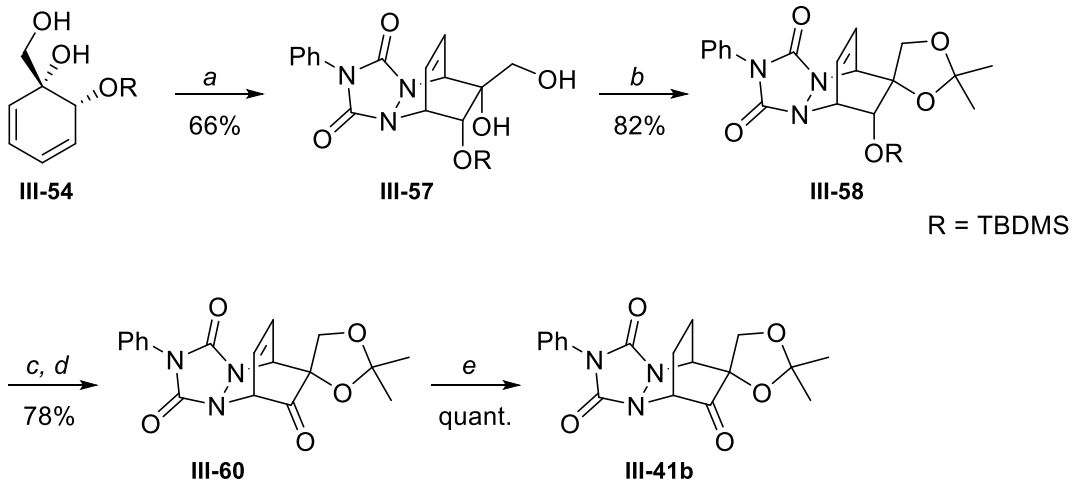
Further investigation into this isomerisation reaction has not yet been conducted, however achieving 100% isomerisation of diol **III-54** to **III-55** may be desirable. Oxidation of the secondary alcohol of **III-55** would in all probability lead to dimerization reaction, providing the (+)-grandifloracin scaffold **III-**

56.[29, 45, 46] (+)-Grandifloracin is known to exhibit activity against pancreatic cancer cells. The described route (scheme III-24) may allow the synthesis of enantiopure (+)-grandifloracin and analogues thereof without the need to employ iron complexation chemistry, as previously required.[47]



Scheme III-24: Proposed synthesis of (+)-grandifloracin scaffold **III-56**.

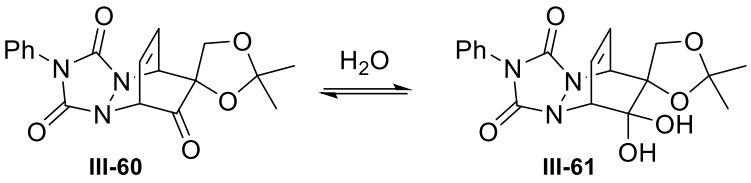
Due to the issues encountered in purifying diol **III-54**, the crude compound was instead telescoped through to the next stage of the synthetic sequence. Diol **III-54** was reacted with PTAD in a cycloaddition reaction, furnishing cycloadduct **III-57** in a good yield. The diastereoselectivity of this reaction was initially assumed based on the TBDMS group blocking the approach of PTAD from the *bottom* face, however this assumption was later found to be false through examination of the X-ray crystal structure of ketone **III-41b** (figure III-25). Subsequent acetonide protection of **III-57** resulted in spiro-cyclic acetonide **III-58**. Removal of the TBDMS group through reaction with TBAF was then achieved, followed by oxidation of the secondary alcohol to give ketone **III-60**. Finally, hydrogenation of the alkene of **III-60** gave ketone **III-41b** in 32% yield from methyl ester **III-21**.



Scheme III-25: Synthesis of ketone **III-41b**. *a*) PTAD (1.0 equiv.), acetone, RT, 3 hours. *b*) *p*TSA (9 mol%), 2,2-DMP, acetone, RT, 5 days. *c*) TBAF (1.05 equiv.), THF, -78°C to RT, 16 hours. *d*) DMSO (10 equiv.), oxalyl chloride (5.0 equiv.), NEt_3 (20 equiv.), CH_2Cl_2, -78°C to RT, 18 hours. *e*) Pd/C, H_2, EtOAc, RT, 16 hours.

Following the purification of unsaturated ketone **III-60** by column chromatography, a notable observation was also made. NMR of the purified material indicated that a significant proportion of ketone hydrate **III-61** (~20%) had been formed (scheme III-26). Whilst it was possible to dehydrate **III-**

61 to re-form ketone **III-60**, this finding suggested that incorporation of the PTAD group increased the electrophilicity of the ketone to the degree that the ketone is susceptible to electrophilic attack from water.

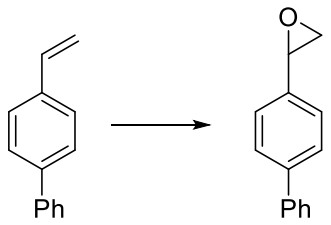


III-60 **III-61**

Scheme III-26: Observed ketone hydrate formed following purification by column chromatography of ketone **III-60**.

With a robust method for the synthesis of ketone **III-41b** developed, quantities of ketone **III-41b** could be synthesised that allow for the optimisation of an organo-catalytic epoxidation procedure using it as an organocatalyst. Reaction optimisation was aimed at maximising substrate conversion. 4-phenylstyrene was selected as the test substrate for reaction optimisation due to its ease of handling and lack of steric bulk around the alkene. Table III-01 details efforts to optimise the reaction conditions, culminating in THF being selected as an ideal solvent with a catalyst loading of 10 mol%. Initial experiments suggest that a lower catalyst loading of ketone **III-41b** can be used for catalytic epoxidation compared to that recommended when employing Shi's catalyst. Upon reaction of ketone **III-41b** with Oxone® ($KHSO_5.½KHSO_4.½K_2SO_4$) and K_2CO_3 in D_2O and CD_3CN at RT for 16 hours, no Baeyer–Villager rearrangement or degradation of ketone **III-41b** was observed. This suggests that ketone **III-41b** may possess higher stability than Shi's catalyst under the reaction conditions, providing a possible explanation for the relatively low catalyst loadings required.

The conditions established for the epoxidation of 4-phenylstyrene using ketone **III-41b** were replicated in the epoxidation of *trans*-stilbene. These substrates were selected because ketone **III-41b** may result in varying enantioselectivities depending on alkene substitution patterns, and HPLC methods for analysis of the epoxide products are well established. A low conversion was observed in the epoxidation of *trans*-stilbene, with a conversion of only a 35% being achieved (determined by ^{1}H NMR). Since *trans*-stilbene and its epoxide I**II-62** could not be separated by column chromatography, chiral HPLC of the mixture was instead conducted. Chiral HPLC concluded that the *e.e.*s of epoxides **III-62** and **III-63** (figure III-10) were ~0%.



Catalyst loading	Solvent	$NBu_4.HSO_4$ (mg)	Oxone® (equiv.)	K_2CO_3 (equiv.)	Temp. (^oC)	Conv.
0 mol%	DMM/MeCN (2:1)	8	7.2	15	25	3%
30 mol%	DMM/MeCN (4:1)	8	2.4	5.0	25	7%
30 mol%	DMM/MeCN (2:1)	8	7.2	15	25	77%
30 mol%	DMM/MeCN/CH_2Cl_2 (2:1:2)	8	7.2	15	25	5%
30 mol%	MeCN	8	7.2	15	25	50%
30 mol%	DMM/MeCN (2:1)	0	7.2	15	25	66%
30 mol%	THF	8	7.2	15	25	88%
30 mol%	THF	8	7.2	15	0	100%
30 mol%	THF	8	7.2	15	35	75%
30 mol%	THF	0	7.2	15	0	100%
10 mol%	THF	0	7.2	15	0	100%

Table III-01: Optimisation of epoxidation using ketone **III-41b** as a catalyst and 4-phenylstyrene as a substrate. Reactions done in 5 mL of organic solvent, with 0.250 mmol of 4-phenylstyrene, for a total reaction time of 14 hours. Conversions calculated by comparison of the integrals of ^1H NMR peaks of the starting material and product.

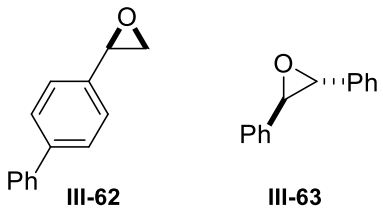


Figure III-10: Structures of epoxides synthesised using ketone **III-41b** as a catalyst.

Due to failure in the enantioselective epoxidation of 4-phenylstyrene and *trans*-stilbene using ketone **III-41b**, the testing of further olefins was deemed unnecessary. The X-ray crystal structures of ketone **III-41b** and alcohol **III-52** (figure III-11) may provide insight as to why ketone **III-41b** failed to epoxidize the tested olefins enantioselectively. Analysis of these two crystal structures is apt since they structurally bear the most similarity to the reactive dioxirane formed when reacting ketone **III-41b** with

Oxone®. As observed in the X-ray crystal structures of ketone **III-41b** and alcohol **III-52**, the PTAD group is seemingly prone to inversion. In the orientation shown in the crystal structure of alcohol **III-41b**, the steric effect exerted by the PTAD group on the catalytically important fragment of the molecule is significantly reduced compared to the orientation adopted in the crystal structure of alcohol **III-52**. During catalysis, should the PTAD of the reactive dioxirane preferentially adopt an orientation similar to that shown in the crystal structure of alcohol **III-52**, the difference in steric bulk between the PTAD group and its opposing CH_2 groups is expected to be minimal, resulting in poor stereocontrol. Whilst the crystal structure of ketone **III-41b** and alcohol **III-52** may not be entirely representative of the structure of the dioxirane in solution, these crystal structures may still be of use in making rational modifications to the ketone that could improve the enantioselectivity during epoxidation reactions.

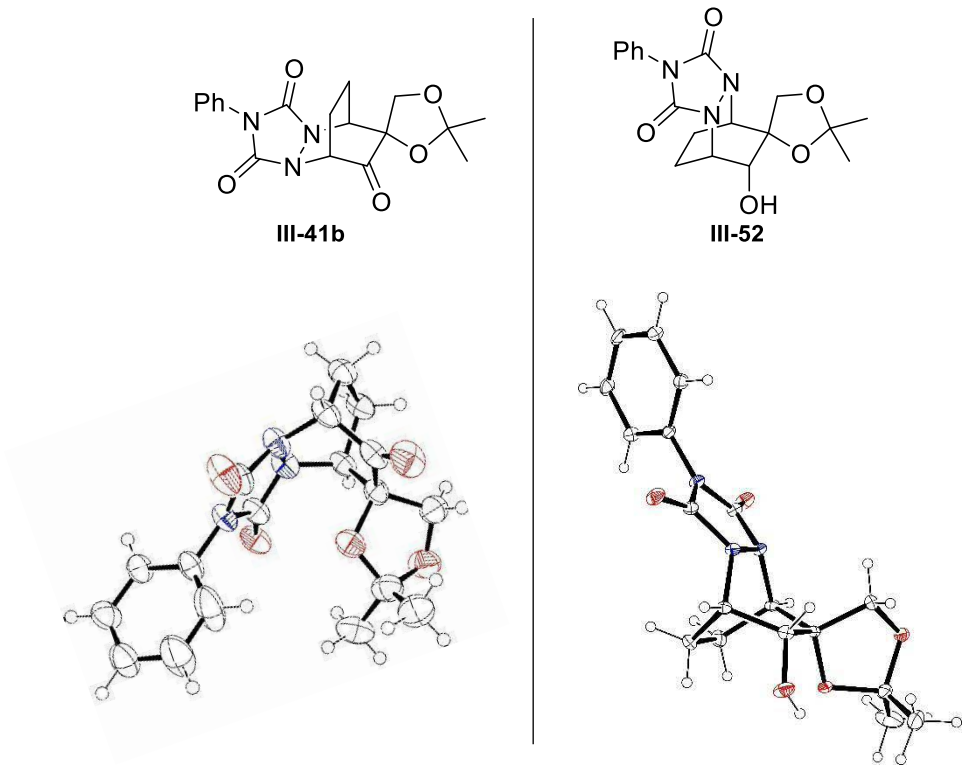
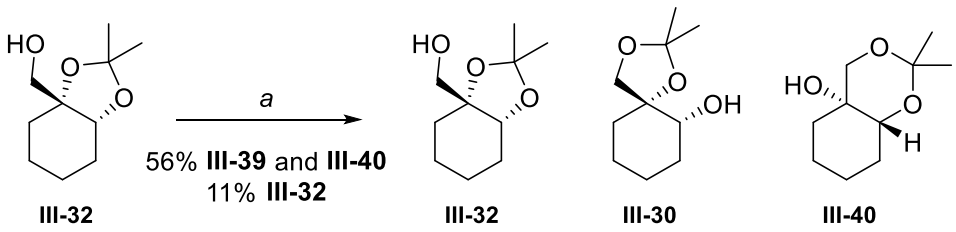


Figure III-11: Single crystal X-ray structure of ketone **III-41b** (left, ellipsoids are shown at 50% probability. Hydrogens are shown as spheres of arbitrary radii. A disordered second molecule of **III-41b** and disordered molecules of solvent in the unit cell have been omitted for clarity) and its analogous alcohol **III-52** (right).

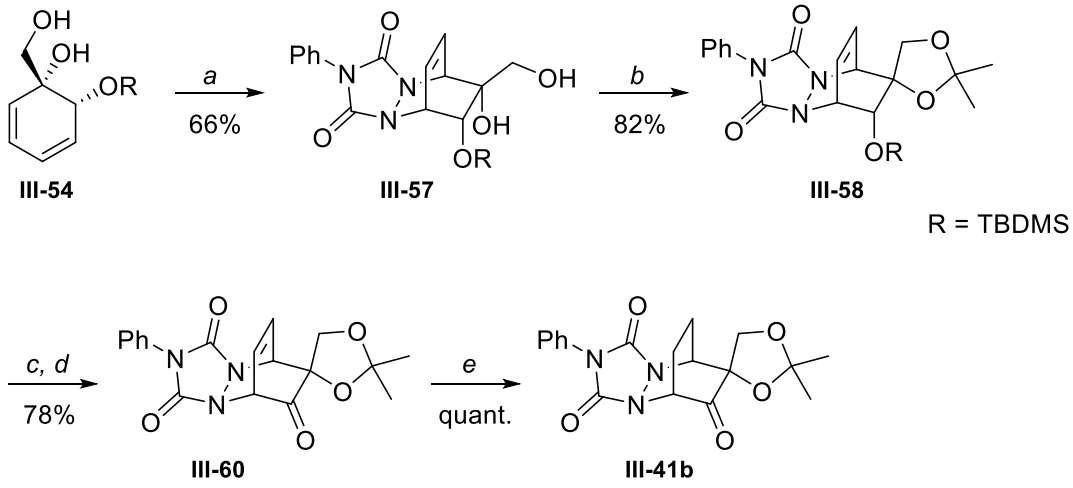
Conclusions and future work

Significant progress has been made in achieving the synthesis of an enantioselective epoxidation catalyst from arene *ipso,ortho*-diol **III-20**. Exploration of this research area commenced with investigation into an acetonide isomerisation reaction, which was believed could be of use in the synthesis of epoxidation catalysts from **III-20**. Acetonide isomerisation conditions were developed, allowing alcohol **III-32** to be isomerised to furnish spiro-acetonide **III-30** along with minor quantities of **III-40** (scheme III-27).



Scheme III-27: Acid catalysed acetonide group migration of alcohol **III-32**. *a*) *p*TSA (1 mol%), MeCN, acetone, 2,2-DMP, RT, 75 minutes.

Utilising this acetonide isomerisation chemistry in the synthesis of target ketone **III-41a**, however, was unsuccessful. Consequentially, an alternative method was employed for its synthesis (scheme III-28), which instead looked to employ a TBDMS ether as a face blocking group in the cycloaddition reaction of diene **III-54** with PTAD. Contrary to this prediction, cycloadduct **III-57** was in fact formed exclusively. Ketone **III-41b** was subsequently synthesised in a total of 8 steps from arene diol **III-20**.



Scheme III-28: Synthesis of target ketone **III-41b**. *a*) PTAD (1.0 equiv.), acetone, RT, 3 hours. *b*) *p*TSA (9 mol%), 2,2-DMP, acetone, RT, 5 days. *c*) TBAF (1.05 equiv.), THF, -78°C to RT, 16 hours. *d*) DMSO (10 equiv.), oxalyl chloride (5.0 equiv.), NEt_3 (20 equiv.), CH_2Cl_2, -78°C to RT, 18 hours. *e*) Pd/C, H_2, EtOAc, RT, 16 hours.

Conditions for olefin epoxidation using ketone **III-41b** were optimised when using 4-phenylstyrene as a substrate, eventually resulting in 100% conversion of the starting material and formation of epoxide

III-62. These conditions were replicated in the epoxidation of *trans*-stilbene to give epoxide **III-63** as well (figure III-12). Enantiomeric excesses of each epoxide were calculated, using HPLC, to be 0%. This finding suggested that significant changes needed to be made to the structure of ketone **III-41b** in order to achieve enantioselectivity in epoxidation reactions.

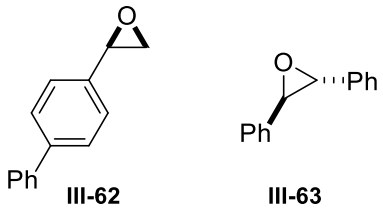
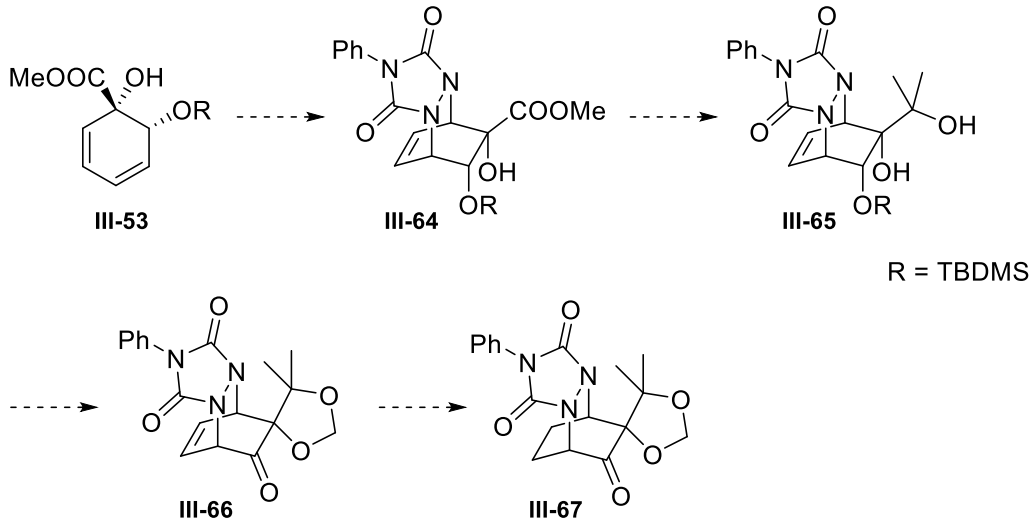


Figure III-12: Structures of epoxides synthesised using ketone **III-41b** as a catalyst.

Ketone **III-67** may be a suitable alternative and a synthetic route to this compound is proposed in scheme III-29. The rationale behind the design of ketone **III-67** is that the newly incorporated methyl groups – installed through reaction of methyl ester **III-64** with MeMgBr or a suitable methylating reagent – may impart a greater steric effect on the *top face* of ketone **III-67**. In addition to this, reaction of diol **III-65** with dimethoxymethane instead if 2,2-dimethoxypropane would result in a diol protecting group that may decrease non-constructive steric hinderance around the ketone moiety.

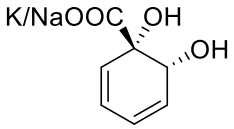


Scheme III-29: Proposed route to revised epoxidation catalyst **III-67**.

Whilst ketone **III-67** may be a good candidate as an asymmetric epoxidation catalyst, there will undoubtedly be other compounds derived from arene diol **III-20** that may also serve this role. Future research into this area could therefore lead to the synthesis of a broad range of poly-functional ketones, some of which may have applications above and beyond organocatalysis.

Experimental

Potassium/sodium (1*S*,6*R*)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate III-20

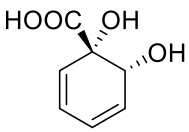


A sterile pipette tip was streaked across a frozen glycerol solution of *Ralstonia eutropha* B9 and added to a sterile solution of Hutner's mineral base (100 mL) and sodium succinate (0.405 g) in an Erlenmeyer flask. The flask was placed on an orbital shaker (250 rpm) at 27°C and shaken for 48 hours. The resulting cloudy suspension was poured into Hutner's mineral base (1.4 L) contained within an Erlenmeyer flask, which was heated to *ca.* 30°C and through which air was bubbled using an airstone. Aqueous D-fructose (10 mL, 10% w/v) was then added, and the culture was left to grow for 24 hours. Following this, the culture was induced with sodium benzoate (1.0 M, 8.0 mL) and fed a further quantity of D-fructose (8.0 mL). After 16 h, repetitive feeding of sodium benzoate and D-fructose began, with a total of 200 mL of sodium benzoate and 200 mL of D-fructose being added to the culture over a period of 5 days (40 mL/ 24 h). A final quantity of D-fructose (20 mL) was then added over the next 24 hours in order to ensure full conversion of all the added substrate.

The culture was centrifuged (5000 rpm, 45 minutes, 4°C) and the supernatant collected. The volume of the supernatant was reduced to ~150 mL through concentration under vacuum. Isopropanol (850 mL) was added, which effected precipitation of a brown solid. The solid was then filtered off, re-dissolved in water (80 mL) and isopropanol (800 mL) added; this was found to aid in the removal of residual media salts and excess D-fructose. The product was again isolated by filtration, washed with CH_2Cl_2 and dried under vacuum to give a cream coloured solid (16.4 g), which contained **III-20** as a mixed sodium/potassium carboxylate salt and a variable proportion of growth medium salts.

^{1}H NMR (500 MHz, DMSO) δ = 5.79 (1H, dd, J = 9.4, 5.2 Hz), 5.73-5.68 (1H, m), 5.61-5.54 (1H, m), 5.51 (1H, d, J = 9.5 Hz), 4.68-4.64 (1H, m). Data are in agreement with those previously reported.[41]

(1*S*,6*R*)-1,6-Dihydroxycyclohexa-2,4-diene-1-carboxylic acid III-21

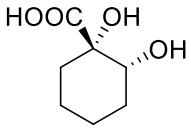


Carboxylate **III-20** (16.4 g, 92.1 mmol (assuming solid contains no residual media salts)) was dissolved in water (1.0 L). The solution was cooled to ~0°C and carefully acidified to between pH 2.5 and 3.0 with aq. conc. HCl. Carboxylic acid **III-21** was extracted with EtOAc (10 x 2.0 L), ensuring the pH of the aqueous phase remained between pH 2.5 and 3.0 after each extraction. The solvent was removed

under vacuum (water bath 30°C), and the product triturated with CH_2Cl_2 (2 x 50 mL) to give pure acid diol **III-21** as an off-white solid (8.00 g, 51.3 mmol, 56%).

^{1}H NMR (500 MHz, CD_3OD) δ = 6.10 (1H, dd, J = 9.7, 5.2 Hz), 5.93 (1H, dddd, J = 9.2, 5.2, 2.8, 1.2 Hz), 5.83-5.76 (2H, m), 4.87-4.82 (1H, m); ^{13}C NMR (126 MHz, CD_3OD) δ = 178.0, 133.6, 127.3, 127.1, 123.5, 75.4, 72.4. Data are in agreement with those previously reported.[39]

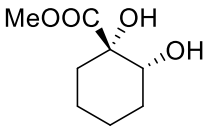
(1*S*,2*R*)-1,2-Dihydroxycyclohexane-1-carboxylic acid II-22



To acid diol **II-21** (5.48 g, 35.1 mmol) and Pd/C (0.700 g) was added MeOH (80 mL). H_2 gas (balloon) was bubbled through the suspension for 23 hours, and the suspension then filtered through Celite. The solvent was removed under vacuum, and the product triturated with cold CH_2Cl_2 (2 x 30 mL) to remove unwanted re-aromatisation products. The off-white solid **III-22** obtained (3.49 g, 21.8 mmol, 62%) was of good purity, meaning that no purification was necessary.

^{1}H NMR (500 MHz, CD_3OD) δ = 3.83 (1H, dd, J = 11.5, 4.5 Hz), 1.81-1.27 (8H, m); ^{13}C NMR (126 MHz, CD_3OD) δ = 179.1, 77.9, 73.6, 35.3, 30.8, 25.4, 21.1. Data are in agreement with those previously reported.[39]

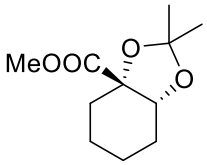
Methyl (1*S*,2*R*)-1,2-dihydroxycyclohexane-1-carboxylate III-23



To a solution of diol acid **II-22** (1.28 g, 8.08 mmol) in MeOH (40 mL) and benzene (40 mL) was added TMS-CHN_2 (~ 12.5 mL, "2M" in hexanes), until a yellow colour persisted in solution. The solution was left to stir for 20 minutes, and the solvent was removed under vacuum. The crude product was purified by column chromatography (30% EtOAc, 70% petroleum ether) to give **III-23** as a white solid (0.975 g, 5.60 mmol, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.87-3.76 (1H, m), 3.81 (3H, s), 3.31 (1H, m, O**H**), 2.02 (1H, s, O**H**), 1.91-1.21 (8H, m). HRMS (ESI+) *m/z* calculated for $(C_8H_{14}O_4Na)$+ 197.0784, found 197.0861. Data are in agreement with those previously reported.[39]

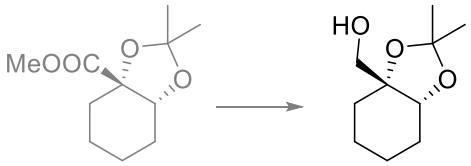
Methyl (3a*S*,7a*R*)-2,2-dimethyltetrahydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate III-24



To diol **III-23** (0.181 g, 1.04 mmol, 1.0 equiv.) in acetone (2.0 mL) was added 2,2-dimethoxypropane (1.2 mL) and *p*TSA (10 mg). The solution was stirred at room temperature for 18 hours. Ethyl acetate (10 mL) was then added, followed by saturated aqueous $NaHCO_3$ (10 mL). The product was extracted with ethyl acetate (4 x 20 mL) and the combined organic layers dried over $MgSO_4$. The solvent was then removed to give **III-24** as a pale yellow oil (0.151 g, 0.705 mmol, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.39 (1H, t, J = 3.4 Hz), 3.79 (3H, s), 2.10-1.96 (2H, m), 1.82 (1H, dddd, J = 14.9, 11.9, 5.8, 3.8 Hz), 1.75-1.35 (5H, m), 1.54 (3H, s), 1.39 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.3, 109.0, 81.1, 75.1, 52.5, 32.4, 28.1, 26.1, 26.0, 20.5, 18.8. Data are in agreement with those previously reported.[39]

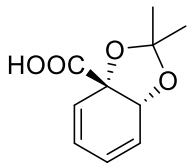
((3a*R*,7a*R*)-2,2-Dimethyltetrahydrobenzo[d][1,3]dioxol-3a(4H)-yl)methanol III-32



To a solution of methyl ester **III-24** (0.205 g, 0.957 mmol, 1.0 equiv.) in anhydrous THF (8 mL), cooled to -78°C, was added $LiBH_4$ (4.0 M in THF, 0.48 mL, 1.92 mmol, 2.0 equiv.) slowly over 2 minutes. The solution was allowed to warm to room temperature over 18 hours. After this time, the reaction was quenched by slow addition of EtOAc (10 mL) followed by water (10 mL). The organic layer was collected and the aqueous phase further extracted with EtOAc (2 x 10 mL). Combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by column chromatography (20% EtOAc, 80% pentane) to give **III-32** as a colourless oil (0.134 g, 0.720 mmol, 75%).

R_f = 0.28 (30% EtOAc, 70% pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.17 (1H, t, J = 2.8 Hz), 3.57 (2H, d, J = 6.6 Hz), 2.17-2.06 (2H, m), 1.69-1.43 (6H, m), 1.51 (3H, s), 1.37 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 107.3, 81.4, 73.3, 64.1, 32.1, 28.6, 27.1, 26.0, 23.0, 20.1; ν_{max} (film) 3459, 2966, 2935, 2864, 1455, 1369, 1201, 1067, 1022, 847 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{10}H_{18}O_3Na)$+ 209.1148, found 209.1151.

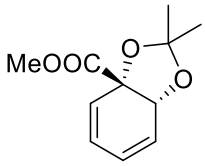
(3a*S*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylic acid III-33



A suspension of diol carboxylate **III-20** (1.90 g, 9.69 mmol, 1.0 equiv.) in 2,2-DMP (70 mL) was cooled to 0°C and TFA (3.7 mL, 48.4 mmol, 5.0 equiv.) added dropwise over 10 minutes. The suspension was allowed to warm to RT over 24 hours and then filtered through a pad of Celite®. The solution was concentrated under vacuum and then resuspended in water (50 mL). The product was extracted with CH_2Cl_2 (2 x 50 mL). Organic extracts were combined, dried over $MgSO_4$ and the solvent removed to give **III-33** as a brown oil (1.69 g, 8.62 mmol, 89%). This brown oil was of acceptable purity to use in subsequent synthetic steps.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.19-6.12 (2H, m), 6.04-6.00 (1H, m), 5.81-5.78 (1H, m), 4.95 (1H, dd, J = 4.1, 0.9 Hz), 1.49 (3H, s), 1.43 (3H, s). HRMS (ESI-) *m/z* calculated for ($C_{10}H_{11}O_4$)- 195.0663, found 195.0674. Data are in agreement with those previously reported.[41]

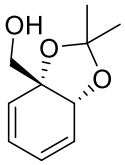
Methyl (3a*S*,7a*R*)-2,2-dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylate III-34



Acid diene **III-33** (1.20 g, 6.10 mmol) was dissolved in MeOH (20 mL) and benzene (20 mL) and TMS-diazomethane (~6 mL, "2M" in hexanes) added slowly until a yellow colour persisted in solution and effervescence ceased. The solution was stirred for 20 minutes, the solvent removed under vacuum and the product purified by column chromatography (15% EtOAc, 85% petroleum ether) to give **III-34** as a colourless oil (0.843 g, 4.01 mmol, 66%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.11-6.02 (2H, m), 6.02-5.93 (1H, m), 5.82-5.74 (1H, m), 4.93 (1H, dd, J = 4.2, 0.7 Hz), 3.75 (3H, s), 1.40 (3H, s), 1.38 (3H, s); HRMS (ESI+) *m/z* calculated ($C_{11}H_{14}O_4Na$)$^+$ 233.0784, found 255.0784. Data are in agreement with those previously reported.[41]

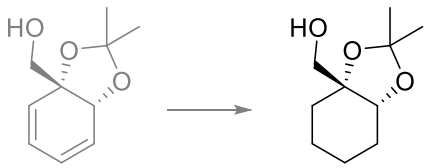
((3a*R*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methanol III-35



Methyl ester **III-34** (1.41 g, 6.71 mmol, 1.0 equiv.) was dissolved in anhydrous THF (15 mL) and cooled to 0°C. $LiBH_4$ (4.0 M in THF, 3.4 mL, 13.4 mmol, 2.0 equiv.) was added dropwise and the solution allowed to warm to room temperature over 16 hours. The reaction was quenched through addition of EtOAc (20 mL) followed by water (20 mL). The organic phase was collected and the product further extracted from the aqueous phase using EtOAc (2 x 20 mL). Organic phases were combined and dried over $MgSO_4$. The solvent was removed under vacuum to give **III-35** as a colourless oil (1.03 g, 0.566 mmol, 84%). The product obtained was of good purity, so no further purification was necessary.

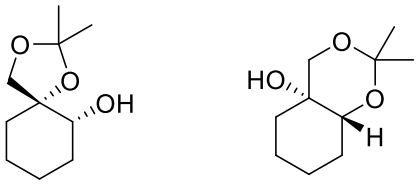
^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.06 (1H, dd, J = 9.7, 5.2 Hz), 6.02-5.95 (2H, m), 5.67 (1H, d, J = 9.9 Hz), 4.46 (1H, d, J = 4.7 Hz), 3.56 (1H, dd, J = 12.0, 2.9 Hz), 3.34 (1H, dd, J = 11.9, 7.1 Hz), 2.22-2.15 (1H, m), 1.42 (3H, s), 1.34 (3H, s); HRMS (ESI+) *m/z* calculated $(C_{10}H_{14}O_3Na)^+$ 205.0835, found 205.0841. Data are in agreement with those previously reported.[41]

((3a*R*,7a*R*)-2,2-Dimethyltetrahydrobenzo[d][1,3]dioxol-3a(4H)-yl)methanol III-32



Through a suspension of diene **III-35** (1.07 g, 5.85 mmol) and Pd/C (11 mg) in MeOH (20 mL) was bubbled H_2 gas (balloon) for 4 hours. The suspension was filtered through Celite® and the solvent removed under vacuum to give **III-32** as a pale yellow oil (1.05 g, 5.64 mmol, 96%) which required no purification. For data, see previous synthetic route to **III-32**.

(5*R*,6*R*)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-ol III-30



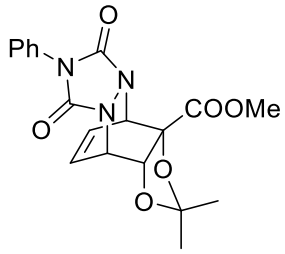
III-30 **III-40**

To primary alcohol **III-32** (1.23 g, 6.63 mmol, 1.0 equiv.) and *p*TSA (13 mg, 0.066 mmol, 1 mol%) was added acetonitrile (20 mL). The solution was stirred for 15 minutes, before acetone (10 mL) and 2,2-

dimethoxypropane (5.0 mL) were added. The solution was stirred for a further hour until TLC (30% EtOAc, 70% pentane) suggested the reaction had reached equilibrium. Sodium acetate (20 mg) was added and the solvent was removed under vacuum. The resulting oil was purified by column chromatography (30% EtOAc, 70% pentane) to give white, crystalline solid, which was found to contain **III-30** and **III-40** (0.697 g, 3.74 mmol, 56%), and starting material **III-32**. Starting material **III-32** was re-subjected to the isomerization conditions outlined above. Following purification by flash column chromatography (30% EtOAc, 70% pentane), another quantity of white crystalline solid was obtained (0.104 g). The products from both isomerization reactions were combined and weighed (0.801 g, 0.430 mmol, 65%). NMR showed the white solid to contain the title compound **III-30** and around 20% of isomerization product **III-40**.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.00 (1H, d, J = 8.4 Hz), 3.73 (1H, d, J = 8.5 Hz), 3.53-3.47 (1H, m), 2.07 (1H, d, J = 6.1 Hz), 1.97 (1H, ddd, J = 13.4, 8.2, 3.5 Hz), 1.86-1.50 (4H, m), 1.42 (3H, s), 1.41 (3H, s), 1.35-1.23 (2H, m); HRMS (ESI+) *m/z* calculated for $(C_{10}H_{18}O_3Na)$+ 209.1148; found 209.1156. Data are in agreement with those previously reported.[39]

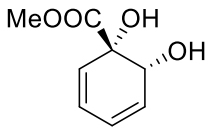
Methyl (3a*S*,4*R*,10*S*,10a*R*)-2,2-dimethyl-6,8-dioxo-7-phenyl-7,8,10,10a-tetrahydro-6H-4,10-etheno[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a(4H)-carboxylate III-42



To methyl ester **III-34** (0.255 g, 1.21 mmol, 1.0 equiv.) in acetone (4.0 mL) was added dropwise a solution of PTAD (0.244 g, 1.39 mmol, 1.15 equiv.) until a red colour persisted in solution. After stirring for 90 minutes, the solvent was removed under vacuum and the resulting red/orange solid was purified by column chromatography (30% EtOAc, 70% pentane) to give **III-42** as a white solid (0.401 g, 1.04 mmol, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.48-7.32 (5H, m), 6.51-6.43 (2H, m), 5.35 (1H, dd, J = 4.2, 3.2 Hz), 5.30 (1H, d, J = 4.2 Hz), 5.22 (1H, q, J = 3.9 Hz), 3.91 (3H, s), 1.36 (3H, s), 1.32 (3H, s); HRMS (ESI+) *m/z* calculated for $(C_{19}H_{19}O_6N_3H)$+ 386.1347; found 386.1350. Data are in agreement with those previously reported.[44]

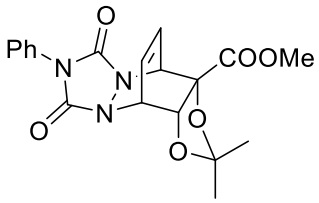
Methyl (1*S*,6*R*)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate III-43



To a solution of diol acid **III-21** (0.546 g, 3.50 mmol) in MeOH (10 mL) and benzene (10 mL) was added TMS-diazomethane (~3.5 mL, "2M" in hexanes) slowly until a yellow colour persisted in solution and effervescence ceased. The yellow solution was stirred for 20 minutes before the solvent was removed under vacuum and the crude product purified by column chromatography (30% EtOAc, 70% petroleum ether → 50% EtOAc, 50% petroleum ether) to give methyl ester **III-43** as a white solid (0.492 g, 2.89 mmol, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.11 (1H, ddt, J = 9.5, 5.3, 0.8 Hz), 5.92 (1H, dddd, J = 9.8, 5.4, 2.8, 1.1 Hz), 5.79 (1H, ddt, J = 9.7, 2.3, 1.0 Hz), 5.74 (1H, dq, J = 9.6, 1.1 Hz), 4.81 (1H, dt, J = 9.0, 2.9 Hz), 3.84 (3H, s), 3.71 (1H, s, O**H**), 3.00 (1H, d, J = 10.2 Hz). HRMS (ESI+) *m/z* calculated for $(C_8H_{10}O_4Na)$+ 193.0471; found 195.0499. Data are in agreement with those previously reported.[48]

Methyl (3a*S*,4*S*,10*R*,10a*R*)-2,2-dimethyl-6,8-dioxo-7-phenyl-7,8,10,10a-tetrahydro-6H-4,10-etheno[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a(4H)-carboxylate III-46

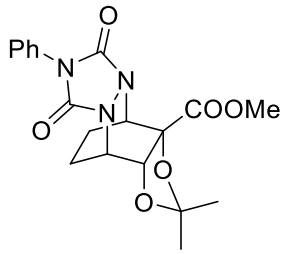


To a solution of diene **III-43** (0.874 g, 5.14 mmol, 1.0 equiv.) in acetone (8.0 mL) was added slowly a solution of PTAD (0.900 g, 5.14 mmol, 1 equiv.) in acetone (8.0 mL) until a red colour persisted. The solution was then allowed to stir at room temperature for 90 mins. The solvent was removed under vacuum to give an orange oil, which was found to contain a mixture of 2 diastereomers (**III-44** and **III-45**). As such, this crude mixture dissolved in acetone (10 mL) and 2,2-dimethoxypropane (10 mL) and *p*TSA (50 mg, 0.263 mmol, 5 mol%) added. The solution was stirred at room temperature for 20 hours. NaOAc (100 mg) was added and the mixture was filtered. The solvent was removed and the product purified by column chromatography (30% EtOAc, 70% pentane → 50% EtOAc, 50% pentane) to give title compound **III-46** (1.31 g, 3.40 mmol, 66%) as a white crystalline solid and its diastereomer **III-42** (0.292 g, 0.758 mmol, 15%) as an off-white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59-7.52 (2H, m), 7.49-7.41 (2H, m), 7.34 (1H, ddt, J = 8.0, 6.8, 1.2 Hz), 6.60 (1H, ddd, J = 8.1, 6.0, 1.2 Hz), 6.50 (1H, ddd, J = 8.1, 6.0, 1.3 Hz), 5.31 (1H, ddd, J = 5.9, 1.3, 0.7 Hz), 5.18 (1H, ddd, J = 6.1, 3.4, 1.3 Hz), 4.87 (1H, dd, J = 3.4, 0.7 Hz), 3.83 (3H, s), 1.53 (3H, s), 1.41 (3H, s);

^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.0, 153.8, 153.3, 131.9, 131.1, 130.2, 129.2, 128.1, 125.2, 117.1, 83.3, 76.2, 54.1, 53.5, 53.0, 26.8, 25.9. Data are in agreement with those previously reported.[44]

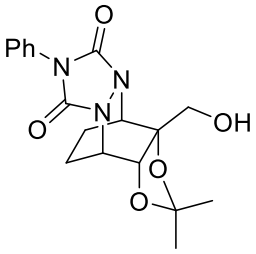
Methyl (3a*S*,4*R*,10*S*,10a*R*)-2,2-dimethyl-6,8-dioxo-7-phenyltetrahydro-6H-4,10-ethano[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a(4H)-carboxylate III-47



Through a suspension of alkene **III-42** (0.401 g, 1.04 mmol) and Pd/C (24 mg) in MeOH (15 mL) was bubbled H_2 gas (balloon). After 72 hours, EtOAc (40 mL) was added to the suspension and it was filtered through a pad of Celite®. The solvent was removed under vacuum to give **III-47** as a white solid (0.358 g, 0.925 mmol, 89%) which required no purification.

R_f = 0.27 (30% EtOAc, 70% pentane); melting point = 200-202°C; $[\alpha]_D^{25}$ = +52 (CH_2Cl_2, *c*. 0.5 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53-7.43 (4H, m), 7.41-7.35 (1H, m), 4.97 (1H, dd, J = 4.5, 1.1 Hz), 4.72-4.65 (2H, m), 3.82 (3H, s), 2.37.2.21 (2H, m), 2.01-1.82 (2H, m), 1.59 (3H, s), 1.30 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 172.2, 152.4, 152.1, 131.6, 129.3, 128.5, 126.2, 112.8, 80.6, 73.5, 53.8, 52.9, 49.7, 26.1, 25.1, 18.1, 17.2; ν_{max} (film) 2994, 2981, 2950, 1764, 1735, 1699, 1410, 1095, 1062, 758 cm^{-1}; HRMS (ESI+) *m/z* calculated for ($C_{19}H_{22}O_6N_3H$)+ 388.1503; found 388.1586.

(3a*R*,4*R*,10*S*,10a*R*)-3a-(Hydroxymethyl)-2,2-dimethyl-7-phenyltetrahydro-6H-4,10-ethano[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-6,8(7H)-dione III-48

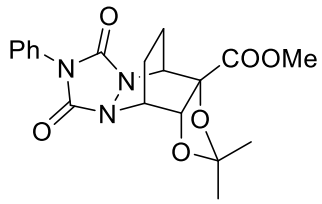


Methyl ester **III-47** (0.170 g, 0.439 mmol, 1.0 equiv.) was dissolved in anhydrous THF (10 mL) and cooled to 0°C. $LiBH_4$ (4.0 M in THF, 0.26 mL, 1.05 mmol, 2.4 equiv.) was added dropwise and the solution allowed to warm to room temperature over 20 hours. At this point, TLC indicated the reaction had not reached completion, so the solution was again cooled to 0°C and a further quantity of $LiBH_4$ (0.13 mL, 0.520 mmol, 1.2 equiv.) added. The reaction was allowed to warm to room temperature over 72 hours. The reaction was then quenched through careful addition of EtOAc (10 mL) followed by water (15 mL). The biphasic solution was extracted with EtOAc (3 x 20 mL). Combined organic

layers were washed with brine (40 mL), dried over $MgSO_4$ and the solvent removed under vacuum to give **III-48** as a white solid (0.155 g, 0.432 mmol, 98%).

R_f = 0.08 (30% EtOAc, 70% petroleum ether); melting point = 189-192°C; $[\alpha]_D^{25}$ = -5 (CH_2Cl_2, *c*. 1 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55-7.45 (4H, m), 7.38 (1H, t, J = 7.3, 1.3 Hz), 4.69 (1H, dd, J = 4.2, 1.6 Hz), 4.60 (1H, dt, J = 4.8, 2.7 Hz), 4.15 (1H, d, J = 4.6 Hz), 3.80 (1H, dd, J = 12.4, 4.9 Hz), 3.70 (1H, dd, J = 12.3, 7.8 Hz), 2.35-2.16 (3H, m, contains O**H**), 1.97 (1H, tt, J = 14.0, 3.5 Hz), 1.84-1.73 (1H, m), 1.58 (3H, s), 1.51 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 152.1, 152.1, 131.6, 129.2, 128.3, 125.6, 112.9, 82.9, 74.7, 65.4, 51.2, 50.8, 27.3, 27.0, 18.3, 18.3; ν_{max} (neat) 3577, 2997, 2982, 2950, 1760, 1702, 1412, 1134, 1035, 744 cm^{-1}; HRMS (ESI+) *m/z* calculated for ($C_{18}H_{22}O_5N_3H$)+ 360.1554, found 360.1556.

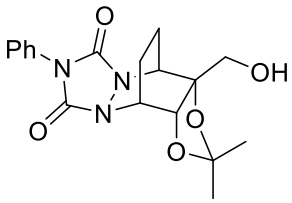
Methyl (3a*S*,4*S*,10*R*,10a*R*)-2,2-dimethyl-6,8-dioxo-7-phenyltetrahydro-6H-4,10-ethano[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a(4H)-carboxylate III-49



Through a suspension of diene **III-46** (0.957 g, 2.48 mmol) and Pd/C (70 mg) in MeOH (40 mL) was bubbled H_2 gas (balloon) for 16 hours. The suspension was filtered through a pad of Celite® and the solvent removed to give a **III-49** as white solid (0.700 g, 1.81 mmol, 73%) which required no further purification.

R_f = 0.18 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = +50 (CH_2Cl_2, *c*. 1.0 g/100 mL); melting point = 211-213°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.63-7.56 (2H, m), 7.49-7.41 (2H, m), 7.33 (1H, tt, J = 7.4, 1.6 Hz), 4.81 (1H, d, J = 3.1 Hz), 4.70-4.64 (2H, m), 3.87 (3H, s), 2.26 (1H, dddd, J = 13.4, 11.1, 4.5, 2.7 Hz), 2.22-2.12 (1H, m), 1.91-1.81 (1H, m), 1.73 (1H, ddt, J = 14.3, 11.6, 2.7 Hz), 1.41 (3H, s), 1.26 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 171.3, 153.4, 151.9, 132.1, 129.2, 127.7, 125.0, 111.1, 82.9, 76.0, 53.5, 51.4, 50.7, 25.5, 24.3, 20.4, 20.0; ν_{max} (film) 2982, 2953, 1772, 1706, 1408, 1267, 1110, 731 cm^{-1}; HRMS (ESI+) *m/z* calculated for ($C_{19}H_{21}O_6N_3H$)+ 388.1503; found 388.1519.

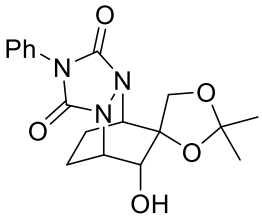
(3a*R*,4*S*,10*R*,10a*R*)-3a-(Hydroxymethyl)-2,2-dimethyl-7-phenyltetrahydro-6H-4,10-ethano[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-6,8(7H)-dione III-50



To a solution of methyl ester **III-49** (0.256 g, 0.661 mmol, 1.0 equiv.) in THF (15 mL), cooled to 0°C, was added $LiBH_4$ (4.0 M in THF, 0.66 mL, 2.64 mmol, 4.0 equiv.) dropwise. The solution was allowed to warm to room temperature over 18 hours. Since TLC indicated the reaction hadn't reached completion, the solution was again cooled to 0°C and a further quantity of $LiBH_4$ (0.41 mL, 1.64 mmol, 2.5 equiv.) was added dropwise. After allowing the solution to again warm to room temperature over 48 hours, the reaction was quenched through careful addition of EtOAc (10 mL) and water (15 mL). The biphasic solution was extracted with EtOAc (5 x 15 mL). Organic layers were combined, dried over $MgSO_4$ and the solvent removed under vacuum. The product was purified by column chromatography (100% EtOAc) to give **III-50** as a white, crystalline solid (0.185 g, 0.515 mmol, 78%).

R_f = 0.18 (100% EtOAc); $[\alpha]_D^{25}$ = +7 (CH_2Cl_2, *c*. 0.28 g/100 mL); melting point = 103-106°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.61-7.55 (2H, m), 7.48-7.42 (2H, m), 7.33 (1H, t, J = 7.4, 1.7 Hz), 4.71 (1H, t, J = 3.0 Hz), 4.66 (1H, ddd, J = 4.8, 3.7, 1.3 Hz), 3.94-3.86 (2H, m), 3.63 (1H, dd, J = 12.2, 9.0 Hz), 2.38-2.05 (4H, m, 1 x O**H**), 1.69-1.55 (1H, m), 1.40 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 153.4, 150.5, 132.1, 129.2, 127.7, 125.2, 110.6, 83.9, 76.4, 66.6, 51.1, 50.9, 26.5, 26.3, 21.3, 20.1; ν_{max} (film) 3443, 2988, 2947, 1761, 1693, 1415, 1209, 1070, 760 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{18}H_{21}O_5N_3H)$+ 360.1554, found 360.1551.

(4*R*,5'*R*,7'*R*,8'*S*)-7'-Hydroxy-2,2-dimethyl-2'-phenyldihydro-1'H,5'H-spiro[[1,3]dioxolane-4,6'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3'(2'H)-dione III-52



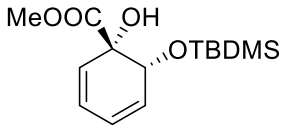
A suspension of alcohol **III-48** (0.481 g, 1.34 mmol, 1.0 equiv.), MeOH (5.0 mL) and aqueous HCl (37%, 0.20 mL) was heated to reflux, at which point full dissolution of alcohol **III-48** was observed. The solution was stirred at reflux for a further 2 hours, before being allowed to cool to room temperature over 1 hour. The solvent was removed under vacuum. Crude ^{1}H NMR of this material showed acetonide deprotection, to form triol **III-51**, had occurred. As such, this product was immediately re-

dissolved in 2,2-dimethoxypropane (10 mL) and was *p*TSA (13 mg, 67 µmol, 5 mol%) added. This solution was stirred at room temperature for 16 hours and the solvent removed under vacuum. The crude product was purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **III-52** as a white, crystalline solid (88 mg, 0.245 mmol, 18%).

R_f = 0.23 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = -9 (CH_2Cl_2, *c*. 0.44 g/100 mL); melting point = 263-265°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55-7.43 (4H, m), 7.40-7.33 (1H, m), 4.43-4.34 (2H, m), 4.27 (1H, t, J = 2.7 Hz), 3.93-3.83 (2H, m), 3.29 (1H, d, J = 6.3 Hz, O**H**), 2.20 (1H, ddt, J = 14.2, 11.6, 3.0 Hz), 2.06 (1H, td, J = 12.2, 5.7 Hz), 1.97-1.85 (1H, m), 1.84-1.68 (1H, m), 1.52 (3H, s), 1.47 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 152.6, 151.9, 131.6, 129.2, 128.3, 125.5, 112.4, 78.8, 72.8, 69.0, 54.4, 52.8, 27.2, 25.4, 19.7, 17.2; ν_{max} (neat) 3490, 2974, 2924, 1757, 1703, 1413, 1277, 1251, 1104, 1056, 737 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{18}H_{21}O_5N_3H)$+ 360.1554, found 360.1560.

Crystal structure data for III-52 can be found in the appendix.

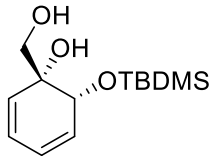
Methyl (1*S*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-hydroxycyclohexa-2,4-diene-1-carboxylate III-53



Diol **III-21** (0.624 g, 3.67mmol, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (10 mL) and cooled to -78°C. NEt_3 (0.61 mL, 4.40 mmol, 1.2 equiv.) was added dropwise followed by TBDMSOTf (0.88 mL, 3.85 mmol, 1.05 equiv.). The resulting solution was stirred at -78°C for 2 hours before being allowed to warm to room temperature over 3 hours. Water (40 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 x 40 mL). Combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and the solvent removed under vacuum. The product was purified by column chromatography (10% EtOAc, 90% petroleum ether) to give **III-53** as a colourless oil (1.03 g, 3.61 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.13 (1H, ddt, J = 9.6, 5.3, 0.8 Hz), 5.96-5.89 (1H, m), 5.81 (1H, dq, J = 9.6, 1.1 Hz), 5.70 (1H, ddt, J = 9.8, 1.9, 0.9 Hz), 4.98 (1H, dddd, J = 2.6, 1.9, 1.3, 0.6 Hz), 3.81 (3H, s), 0.90 (9H, s), 0.12 (3H, s), 0.04 (3H, s); HRMS (ESI+) *m/z* calculated for $(C_{14}H_{24}O_4SiNa)$+ 307.1336, found 307.1379. Data are in agreement with those previously reported.[47]

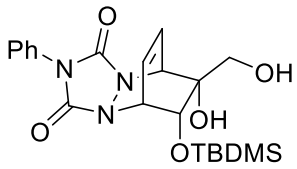
(1*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-(hydroxymethyl)cyclohexa-2,4-dien-1-ol III-54



A solution of methyl ester **III-53** (0.464 g, 1.63 mmol, 1.0 equiv.) in anhydrous THF (15 mL) was cooled to 0°C and $LiBH_4$ (4.0 M in THF, 0.82 mL, 3.26 mmol, 2.0 equiv.) was added slowly over 5 minutes. The solution was allowed to warm to room temperature over 16 hours and the reaction quenched through careful addition of EtOAc (25 mL) followed by water (25 mL). The organic layer was collected and the aqueous layer further extracted with EtOAc (2 x 25 mL). Combined organic phases were dried over $MgSO_4$ and the solvent removed under vacuum to give **III-54** as a pale yellow oil (0.353 g, 1.38 mmol, 85%). Crude ^{1}H NMR indicated that this material consisted of title compound **III-53** along with a minute quantity of unidentifiable impurities. Attempted purification of this compound by column chromatography (30% EtOAc, 70% petroleum ether) resulted in minor formation (~15%) of a compound which was inseparable from title compound **III-54**. As such, the crude material was used in the synthesis of **III-54** without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.00-5.87 (2H, m), 5.82-5.73 (1H, m), 5.72-5.64 (1H, m), 4.35 (1H, d, J = 4.3 Hz), 3.53 (1H, d, J = 11.3 Hz), 3.42 (1H, d, J = 11.4 Hz), 3.32 (1H, s, O**H**), 0.91 (9H, s), 0.13 (3H, s), 0.12 (3H, s); *m/z* calculated for $(C_{13}H_{24}O_3SiNa)$+ 279.1387, found 279.1423.

(5*R*,8*S*,10*R*,11*R*)-11-((*tert*-Butyldimethylsilyl)oxy)-10-hydroxy-10-(hydroxymethyl)-2-phenyl-5,8-dihydro-1H-5,8-ethano[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione III-57

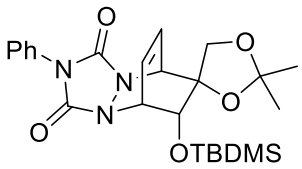


To a solution of diene **III-54** (0.657 g, 2.57 mmol, 1.0 equiv.) in acetone (15 mL) was added a solution of PTAD (0.449 g, 2.57 mmol, 1.0 equiv.) in acetone (10 mL) slowly until a red colour persisted in solution. The solution was stirred for a further 3 hours before the solvent was removed under vacuum. The crude product was purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **III-57** as a white solid (0.731 g, 1.70 mmol, 66%).

R_f = 0.32 (75% EtOAc, 25% petroleum ether); melting point = 170-173°C; $[\alpha]_D^{25}$ = -14 (CH_2Cl_2, *c*. 1 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50-7.41 (4H, m), 7.37-7.32 (1H, m), 6.55 (1H, ddd, J = 8.2, 5.8, 1.5 Hz), 6.46 (1H, ddd, J = 8.2, 5.9, 1.6 Hz), 5.00 (1H, dd, J = 5.9, 1.6 Hz), 4.84 (1H, ddd, J = 6.0, 2.6, 1.5 Hz), 3.61 (1H, d, J = 2.6 Hz), 3.45 (1H, dd, J = 11.5, 7.8 Hz), 3.35 (1H, dd, J = 11.4, 5.8 Hz), 2.26 (1H, dd, J =

7.9, 6.0 Hz), 0.95 (9H, s), 0.25 (3H, s), 0.19 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 154.8, 131.8, 131.5, 129.2, 129.0, 128.3, 125.6, 70.6, 68.4, 67.5, 56.3, 56.0, 25.8, 18.2, -4.3, -4.8; ν_{max} (film) 3555, 3426, 2955, 2928, 2858, 1764, 1695, 1413, 1253, 1097, 833 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{21}H_{29}O_5N_3SiNa)$+ 454.1769; found 454.1817.

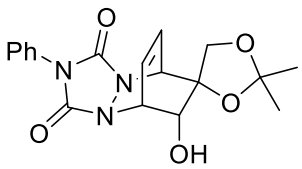
(4*R*,5'*R*,8'*S*,11'*R*)-11'-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-2'-phenyl-5',8'-dihydro-1'H-spiro[[1,3]dioxolane-4,10'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3'(2'H)-dione III-58



A solution of diol **III-57** (0.685 g, 1.59 mmol, 1.0 equiv.) and *p*TSA (28 mg, 0.147 mmol, 9 mol%) in 2,2-dimethoxypropane (20 mL) and acetone (10 mL) was stirred at room temperature for 5 days. After this time, the reaction mixture was poured in saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). Combined organic layers were dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by recrystallisation with the minimum amount of hot EtOAc. Addition of petroleum ether was found to aid crystallisation of the product. **III-58** was obtained as a white solid (0.613 g, 1.30 mmol, 82%).

R_f = 0.32 (50% EtOAc, 50% petroleum ether); melting point = 198-201°C; $[\alpha]_D^{25}$ = -5.0 ($CHCl_3$, *c*. 1 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.47-7.40 (4H, m), 7.36-7.31 (1H, m), 6.53-6.44 (2H, m), 4.88 (1H, dt, J = 5.6, 2.1 Hz), 4.80 (1H, dd, J = 5.5, 1.9 Hz), 3.85 (1H, d, J = 9.4 Hz), 3.72 (1H, d, J = 2.4 Hz), 3.69 (1H, d, J = 9.3 Hz), 1.60 (3H, s), 1.43 (3H, s), 0.95 (9H, s), 0.20 (3H, s), 0.17 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.2, 154.8, 131.8, 130.7, 130.4, 129.2, 128.2, 125.8, 112.0, 77.6, 73.3, 69.7, 57.8, 56.9, 27.8, 26.3, 26.0, 18.4, -4.3, -4.3; HRMS (ESI+) *m/z* calculated for $(C_{24}H_{33}O_5N_3SiNa)$+ 494.2082, found 494.2083.

(4*R*,5'*R*,8'*S*,11'*R*)-11'-Hydroxy-2,2-dimethyl-2'-phenyl-5',8'-dihydro-1'H-spiro[[1,3]dioxolane-4,10'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3'(2'H)-dione III-59

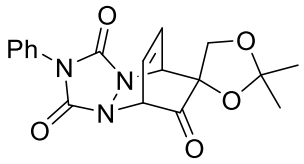


A solution of silyl protected alcohol **III-58** (0.607 g, 1.29 mmol, 1.0 equiv.) in anhydrous THF (20 mL) was cooled to -78°C. TBAF (1.0 M in THF, 1.35 mL, 1.35 mmol, 1.05 equiv.) was added dropwise and the solution stirred at -78°C for 1 hour, before being allowed to warm to room temperature over 16 hours. EtOAc (5.0 mL) was added, followed by saturated aqueous $NaHCO_3$ (5.0 mL) and water (15 mL).

The biphasic solution was extracted with EtOAc (3 x 20 mL). Organic layers were combined, washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **III-59** as a white solid (0.413 g, 1.16 mmol, 90%).

R_f = 0.17 (50% EtOAc, 50% petroleum ether); melting point = 190-193°C; $[\alpha]_D^{25}$ = -9.0 (CH_2Cl_2, *c*. 0.5 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ =7.47-7.41 (4H, m), 7.37-7.33 (1H, m), 6.57-6.54 (2H, m), 5.02 (1H, dt, J = 5.1, 2.4 Hz), 4.81 (1H, dd, J = 5.2, 2.1 Hz), 3.95 (1H, d, J = 9.6 Hz), 3.80 (1H, d, J = 9.6 Hz), 3.64 (1H, dd, J = 7.3, 2.6 Hz), 3.33 (1H, d, J = 7.3 Hz), 1.62 (3H, s), 1.47 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.5, 154.9, 131.5, 131.4, 129.7, 129.2, 128.3, 125.6, 112.7, 77.0, 73.5, 68.5, 57.3, 56.7, 27.1, 25.5; ν_{max} (film) 3554, 2998, 2941, 2891, 1763, 1708, 1406, 1082, 767 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{18}H_{19}O_5N_3Na)$+ 380.1217; found 380.1206.

(4*R*,5'*S*,8'*R*)-2,2-Dimethyl-2'-phenyl-5',8'-dihydro-1'H-spiro[[1,3]dioxolane-4,11'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3',10'(2'H)-trione III-60



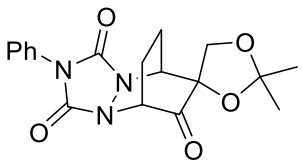
A solution of DMSO (0.82 mL, 11.5 mmol, 10 equiv.) in CH_2Cl_2 (30 mL) was cooled to -78°C and oxalyl chloride (0.49 mL, 5.75 mmol, 5.0 equiv.) added dropwise. This solution was stirred at -78°C for 30 minutes before alcohol **III-59** (0.413 g, 1.16 mmol, 1.0 equiv.) was added dropwise. After stirring at -78°C for 1 hour, NEt_3 (3.19 mL, 23.0 mmol, 20 equiv.) was added dropwise. The solution was stirred at -78°C for a final hour before the reaction was allowed to warm to room temperature over 16 hours. The solution was poured into EtOAc (60 mL) and the organic phase washed with saturated aqueous NH_4Cl (60 mL), water (60 mL), saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was purified by column chromatography (50% EtOAc, 50% petroleum ether → 75% EtOAc, 25% petroleum ether) to give a white solid. Due to the propensity of ketone **III-60** to form its corresponding hydrate, it was then necessary to stir this solid in anhydrous CH_2Cl_2 (10 mL) with molecular sieves for 3 days. Removing the solvent under vacuum resulted in the isolation of a white solid (0.390 g, 1.01 mmol, 87%) which was shown to be pure ketone **III-60**.

R_f = 0.39 (50% EtOAc, 50% petroleum ether); melting point = 157-160°C; $[\alpha]_D^{26}$ = +158 ($CHCl_3$, *c*. 1.0 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50-7.42 (4H, m), 7.41-7.37 (1H, m), 6.81 (1H, ddd, J = 8.2, 6.0, 1.6 Hz), 6.70 (1H, ddd, J = 8.2, 6.1, 1.9 Hz), 5.21 (1H, dd, J = 6.1, 1.6 Hz), 5.10 (1H, dd, J = 6.0, 1.9 Hz), 4.19 (1H, d, J = 9.4 Hz), 3.80 (1H, d, J = 9.4 Hz), 1.58 (3H, s), 1.49 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$)

δ = 194.5, 155.3, 154.0, 134.9, 131.4, 129.4, 129.2, 128.8, 125.7, 114.4, 78.2, 71.4, 59.7, 59.2, 27.1, 25.4; ν_{max} (film) 3097, 3032, 2993, 2938, 1772, 1749, 1706, 1405, 1275, 1055, 753 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{19}H_{21}O_6N_3Na)+$ 410.1323; found 410.1346.*

*mass calculated and found is for the hemi-ketal formed through attack of MeOH on the ketone moiety of **III-60**.

(4*R*,5'*S*,8'*R*)-2,2-Dimethyl-2'-phenyl-1'H,5'H-spiro[[1,3]dioxolane-4,6'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3',7'(2'H,8'H)-trione III-41b

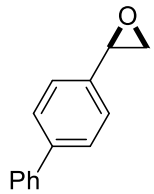


Through a suspension of alkene **III-60** (0.375 g, 1.06 mmol) and Pd/C (80 mg) in EtOAc (20 mL) was bubbled H_2 gas (balloon) for 16 hours. The suspension was then filtered through a pad of Celite® and the solvent removed under vacuum to give **III-41b** as a white solid (0.378 g, 1.06 mmol, 100%). This solid required no further purification.

R_f = 0.25 (50% EtOAc, 50% petroleum ether); melting point = 185-187°C; $[\alpha]_D^{27}$ = -96 ($CHCl_3$, *c*. 1.0 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.50-7.42 (4H, m), 7.41-7.36 (1H, m), 4.68 (1H, t, J = 2.9 Hz), 4.57 (1H, dd, J = 4.5, 1.3 Hz), 4.34 (1H, d, J = 9.3 Hz), 4.07 (1H, d, J = 9.3 Hz), 2.54-2.39 (2H, m), 2.24-2.12 (1H, m), 1.84-1.71 (1H, m), 1.46 (3H, s), 1.39 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 200.7, 156.2, 152.9, 131.7, 129.4, 128.5, 125.9, 114.2, 82.7, 66.8, 59.2, 56.3, 26.8, 25.3, 23.3, 20.2; ν_{max} (film) 3040, 2994, 2948, 2892, 1757, 1704, 1413, 1140, 1050, 861 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{18}H_{19}O_5N_3Na)+$ 380.1217; found 380.1218.

Crystal structure data for III-41b can be found in the appendix.

2-([1,1'-Biphenyl]-4-yl)oxirane III-62



A solution of THF (5.0 mL) and aq. Na_2EDTA (0.4 mM, 2.0 mL) was cooled to 0°C and 4-phenylstyrene (45 mg, 0.250 mmol, 1.0 equiv.) added, followed by ketone **III-41** (9 mg, 25.2 μmol, 10 mol%). Solutions of Oxone® (50% $KHSO_5$, 1.107 g, 0.360 mmol, 7.2 equiv.) in aq. Na_2EDTA (0.4 mM, 8.0 mL) and K_2CO_3 (0.519 g, 3.76 mmol, 15 equiv.) in aq. Na_2EDTA (0.4 mM, 8.0 mL) were added simultaneously by syringe over 6 hours, whilst maintaining the reaction temperature at 0°C. Over the following 8 hours, the

reaction was allowed to warm to room temperature. Water (20 mL) was added to the reaction and the aqueous phase extracted with EtOAc (3 x 20 mL). Combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent removed under vacuum. ^{1}H NMR of the crude product showed full conversion of the starting material to product **III-62**. The crude product was purified by column chromatography (5% Et_2O, 5% NEt_3, 90% petroleum ether) to give **III-62** as a white solid (37 mg, 0.189 mmol, 76%). HPLC analysis of the product was conducted using a Chiralcel OD column (250 mm) with a mixture of 90% hexane, 10% isopropanol used as an eluent (1.2 mL/min flow rate). Retention times of the synthesised enantiomers of **III-62** were 4.5 minutes and 5.0 minutes, with both being detected using U.V. light (254 nm). The product was shown to be racemic.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.62-7.56 (4H, m), 7.45 (2H, tt, J = 7.0,0.7 Hz), 7.39-7.33 (3H, m), 3.92 (1H, dd, J = 4.1, 2.6 Hz), 3.19 (1H, dd, J = 5.5, 4.1 Hz), 2.86 (1H, dd, J = 5.5, 2.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.2, 140.7, 136.6, 128.8, 127.4, 127.3, 127.1, 126.0, 52.2, 51.2. Data are in agreement with those previously reported.[49]

2,3-Diphenyloxirane

A solution of THF (5.0 mL) and aq. Na_2EDTA (0.4 mM, 2.0 mL) was cooled to 0°C and *trans*-stilbene (45 mg, 0.250 mmol, 1.0 equiv.) added, followed by ketone **III-41** (9 mg, 25.2 µmol, 10 mol%). Solutions of Oxone® (50% $KHSO_5$, 1.107 g, 0.360 mmol, 7.2 equiv.) in aq. Na_2EDTA (0.4 mM, 8.0 mL) and K_2CO_3 (0.519 g, 3.76 mmol, 15 equiv.) in aq. Na_2EDTA (0.4 mM, 8.0 mL) were added simultaneously by syringe over 6 hours, whilst maintaining the reaction temperature at 0°C. Over the following 8 hours, the reaction was allowed to warm to room temperature. Water (20 mL) was added to the reaction and the aqueous phase extracted with EtOAc (3 x 20 mL). Combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and the solvent removed under vacuum. ^{1}H NMR of the crude product showed incomplete conversion of the starting material to product **III-63** (41 mg), however separation of the starting material and the epoxide product by column chromatography was not possible. HPLC analysis of the crude product was conducted using a Chiralcel OD column (250 mm) with a mixture of 90% hexane, 10% isopropanol used as an eluent (1.0 mL/min flow rate). Retention times of the synthesised enantiomers of **III-63** were 5.60 minutes and 7.68 minutes, with both being detected using U.V. light (220 nm). The product was shown to be racemic.

Data are in agreement with those previously reported.[21]

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Exploiting a fluoro-arene *ipso,ortho*-diol in synthesis

An introduction to fluoro-alkenes and substituted arene diols

The biology of fluorine containing compounds has been subject to intense research over the last few decades, primarily due to the significant effect that fluorine can have on a compound's biological activity and stability. These affects have been documented in a number of comprehensive reviews.[1-3] The changes in, for example, membrane permeability, log P, pK_a, and metabolic stability that fluorine can confer has resulted in fluorine containing compounds garnering widespread use as pharmaceuticals. Maraviroc (figure IV-01, prescribed as an antiretroviral drug in the treatment of H.I.V.)[4, 5] and Tafluprost (figure IV-01, prescribed to treat open-angle glaucoma)[6] are just two examples of fluorine containing pharmaceuticals. Aside from the biological significance of fluorination chemistry, fluorine containing molecules have also been used widely in liquid crystal displays of smart phones, further demonstrating their application.[7]

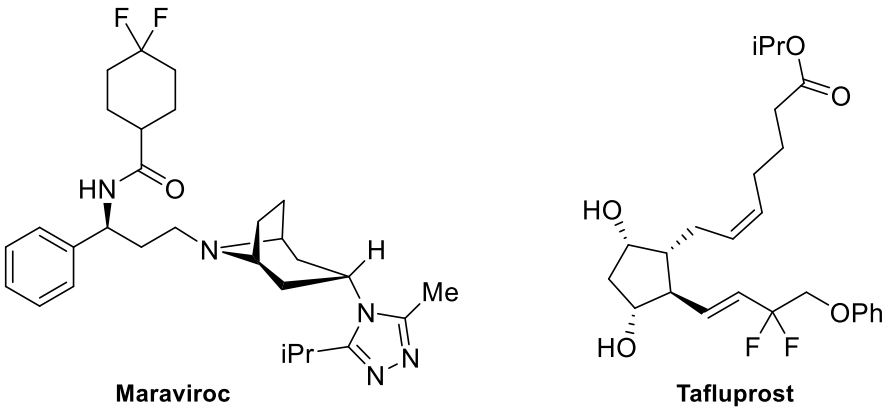
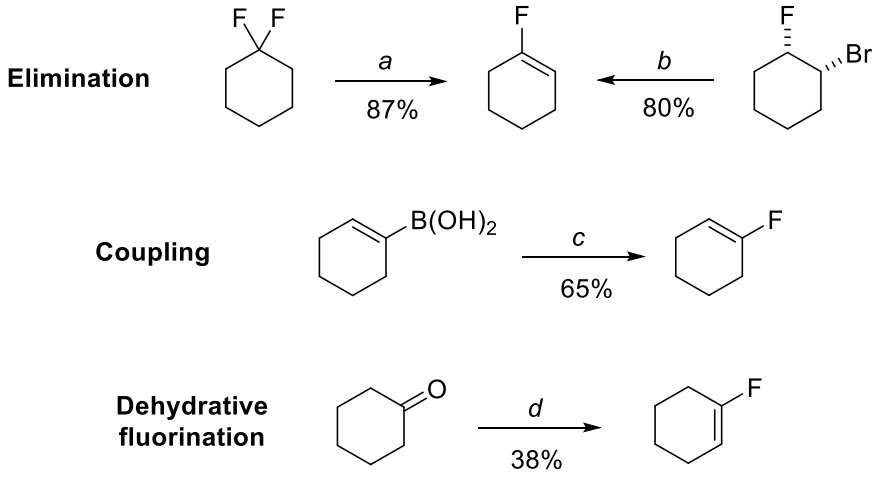


Figure IV-01: Structures of Maraviroc (left) and Tafluprost (right).

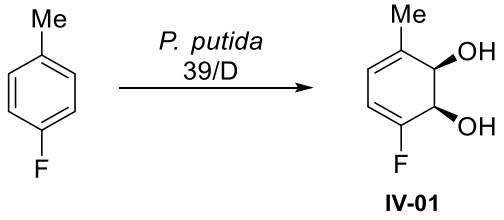
Fluoro-alkenes specifically have been reported to act as isosteric and isopolar amide mimics,[8] whilst still exhibiting distinct biophysical properties from amides. For example, fluoro-alkenes have decreased hydrogen bonding donating and accepting capabilities relative to amides,[9] whilst also being non-hydrolysable, thus conferring greater metabolic stability.

The chemical and biological utility of fluoro-alkenes has consequently led to interest in their synthesis. A variety of methods are now available for the synthesis of acyclic fluoro-alkenes, which have been comprehensively documented by Hara.[10] Strategies for the synthesis of cyclic fluoro-alkenes are less established, however. This is most commonly achieved by 1 of 3 methods (scheme IV-01): elimination reactions,[11] coupling reactions[12, 13] or the dehydrative fluorination of cyclohexanones.[14]



Scheme IV-01: Methods of 1-fluoro-cylcohexene synthesis. *a*) *t*-BuOK, acetone, 85°C. *b*) *t*-BuOK, *t*-BuOH, 70°C. *c*) NaOH, AgOTf, Selectfluor, RT. *d*) DAST, H_2SO_4, diglyme, RT.[11, 12, 14]

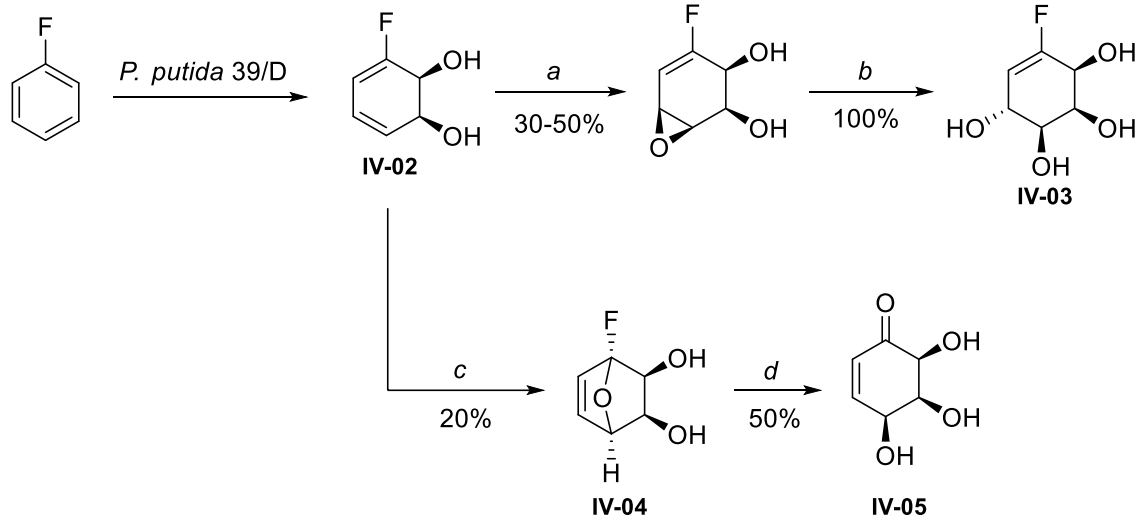
Microbial oxidation of fluoro-aromatics offers the scalable and environmentally benign synthesis of enantiopure cyclic fluoro-alkenes (and, through derivatisation, of organofluorine compounds in general). The first paper documenting this transformation was published by Gibson in 1977.[15] Gibson achieved the *ortho, meta*-dihydroxylation of 4-fluorotoleune using *Pseudomonas putida* 39/D – a bacterium known to express the TDO enzyme (scheme IV-02). One of Gibson's research aims was to ascertain the effect of 4-halo substituents on the enantioselectivity in the microbial oxidation of toluenes. It was tentatively concluded that the enantioselectivity in the microbial oxidation of 4-fluorotoluene did not differ from the enantioselectivity observed when using toluene as a substrate, with diol **IV-01** being produced. This was conclusively confirmed by Boyd in 1991 after analysing the crystal structure of a derivative of diol **IV-01**.[16] The microbial *ortho, meta*-dihydroxylation of several other fluoro-aromatics has subsequently been reported, including 4-fluoro-iodobenzene[17] and fluorobenzene.[18, 19]



Scheme IV-02: Microbial oxidation of 4-fluorotoluene with *Pseudomonas putida* 39/D.

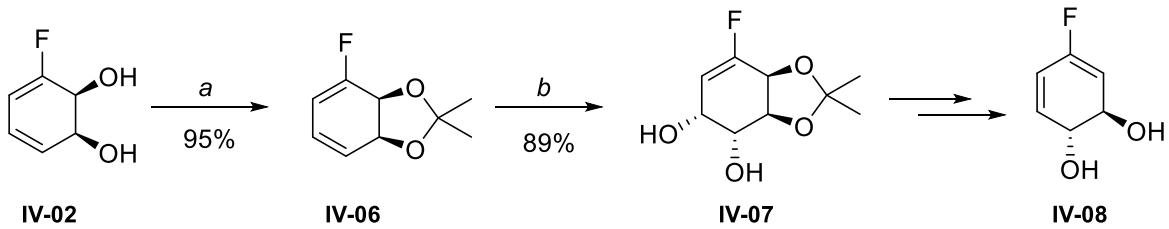
One of the first published examples of a fluoro-arene diol being used in synthesis was reported by Carless in 1990. Carless' work predominantly focussed on epoxidation reactions of fluoro-arene diol **IV-02**, leading to the synthesis of 6-fluoro-conduritol, **IV-03**, from fluorobenzene (scheme IV-03). Cyclitols in general are known to possess a diverse range of biological functions,[20, 21] and addition of fluorine may alter their function, making Carless' work of interest to synthetic and medicinal chemists.

Furthermore, Carless also exploited the tendency of α-fluoro-alcohols to spontaneously eliminate fluoride in the synthesis of enone **IV-05**, which was achieved through the ring opening of fluoro-furan **IV-04** with water.



Scheme IV-03: Elaboration of fluoro-arene diol **IV-02** demonstrated by Carless.[18] *a*) *m*CPBA, CH_2Cl_2, RT. *b*) water. *c*) *m*CPBA, Na_2CO_3, CH_2Cl_2, RT. *d*) TFA, water, acetone, RT.

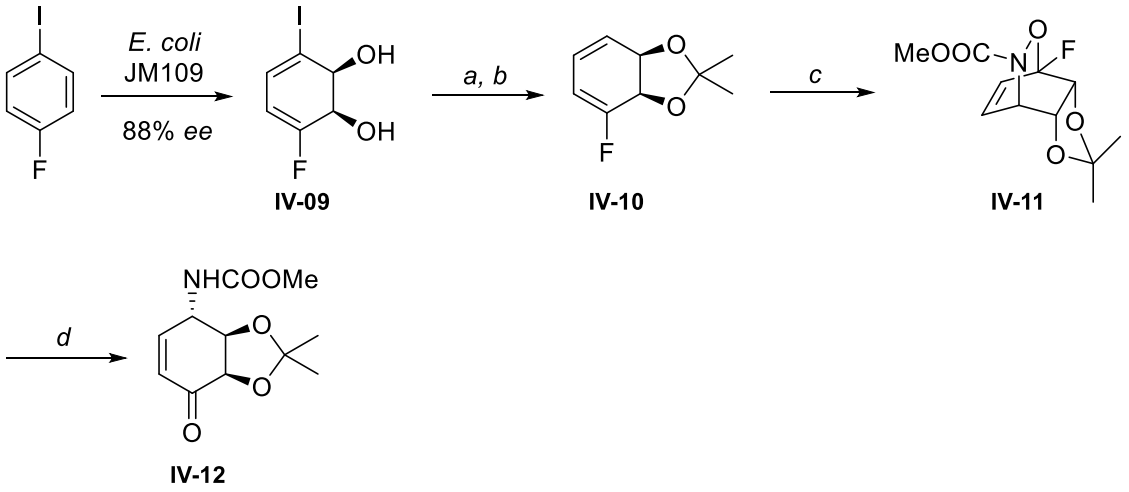
Further research into the synthetic utility of fluoro-arene *ortho, meta*-diols was conducted by Boyd in the early 21st century.[22, 23] Similarly to Carless, Boyd too chose to focus on oxidative transformations of fluoro-arene *ortho, meta*-diol **IV-02**; however, Boyd and co-workers researched the dihydroxylation of these compounds. They reported that the dihydroxylation of **IV-06** was both regioselective for the non-fluorinated alkene and stereoselective, resulting in **IV-07** (scheme IV-04). Boyd subsequently demonstrated how this diol could be transformed further to access fluoro-arene *trans*-diol **IV-08**.



Scheme IV-04: Dihydroxylation of fluoro-arene diol **IV-06**, and subsequent transformation to fluoro-arene trans-diol **IV-08**. *a*) *p*TSA, 2,2-DMP, acetone, 0°C to RT. *b*) OsO_4, NMO, acetone, water, RT.

Hudlický has also conducted research into fluoro-arene *ortho, meta*-diols.[24] Hudlický, instead of conserving the fluorine, exploited its innate reactivity in the attempted synthesis of *ent*-7-deoxypancratistatin, **IV-12**. Following its production through the microbial oxidation of 4-fluoroiodobenzene, diol **IV-09** was protected as an acetonide (scheme IV-05). A Diels–Alder reaction of fluoro-diene **IV-10** with methyl hydroxycarbamate was subsequently conducted, which is reported to have afforded cycloadduct **IV-11** (scheme IV-06). Treating **IV-11** with mercury/sodium amalgam

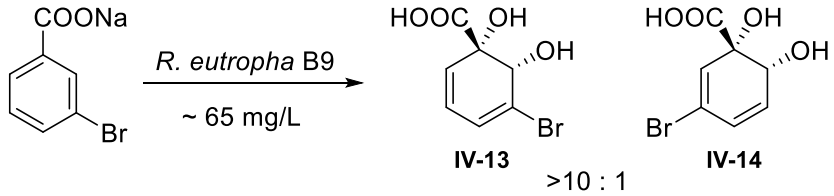
reportedly gave γ-amino-enone **IV-12** (scheme IV-05). This is likely to have arisen from the reductive cleavage of the N–O bond, followed by immediate elimination of fluoride from the resulting α-fluoro-hydroxyl group.



Scheme IV-05: First stages of Hudlický's attempted synthesis of *ent*-7-deoxypancratistatin when using fluoro-arene diol **IV-09** as a starting material.[24] *a*) Bu_3SnH, AIBN, THF. *b*) *p*TSA, 2,2-DMP. *c*) $HONHCO_2Me$, $NaIO_4$, H_2O, MeOH. *d*) Na(Hg), THF, H_2O. Yields and reaction temperatures not reported.

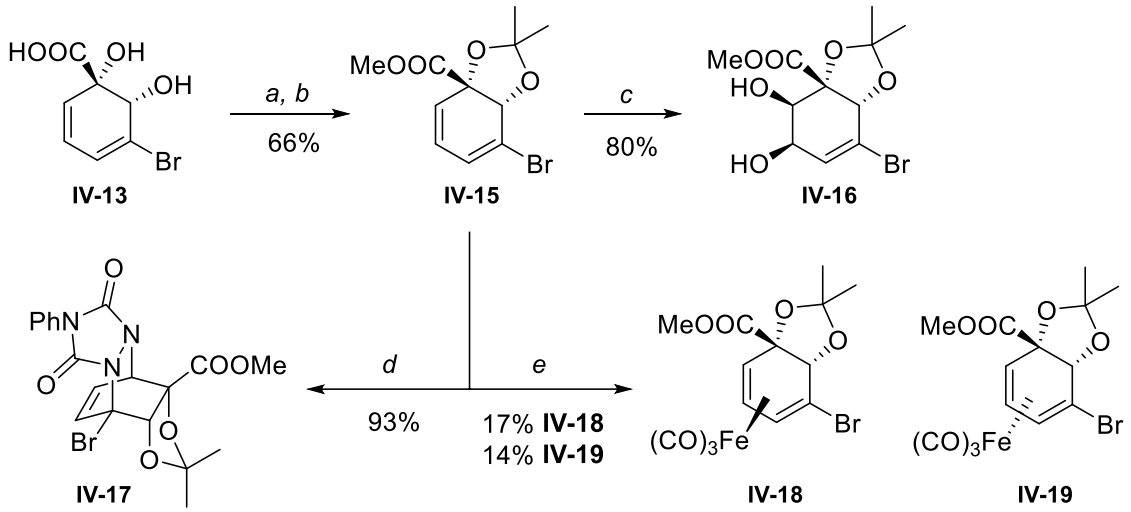
Whilst the microbial oxidation of a range of substituted benzoic acids – including fluoro-benzoic acids - has also been achieved in the past, [25-27] little synthetic chemistry has been conducted on their resulting arene diols. To the best of our knowledge, there are only 2 examples of substituted arene *ipso, ortho*-diols being used in synthesis.[28, 29] A contributing factor to the lack of literature in this area is likely the poor substrate scope of the BZDO enzyme; substituted benzoic acids are known to be microbially oxidized at a significantly slower rate their non-substituted counterparts, resulting in substrate yields that may not be considered synthetically useful.[30]

Nonetheless, in 2009 Lewis *et al.* reported the microbial oxidation of sodium 3-bromobenzoate (scheme IV-06).[28] Depending on the orientation of sodium 3-bromobenzoate in the active site of the BZDO enzyme, two regioisomeric products may be obtained through this biotransformation: **IV-13** and **IV-14**. Lewis *et al.* found that the formation of bromo-arene diol **IV-13** predominated.



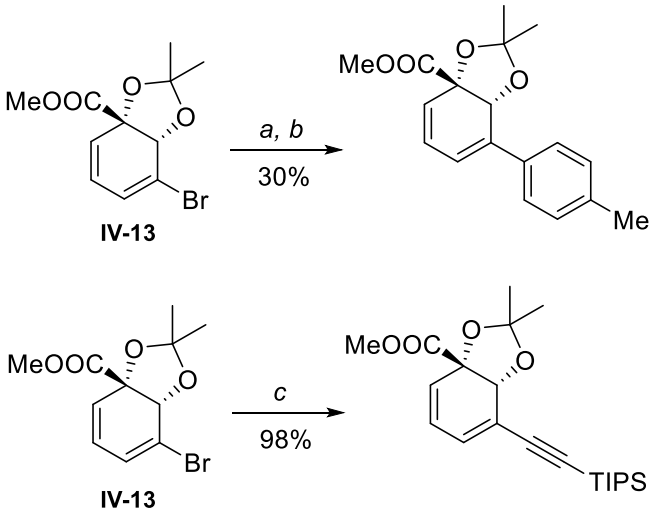
Scheme IV-06: Microbial oxidation of sodium 3-bromobenzoate.[28]

Uses of bromo-arene diol **IV-13** in synthesis were then investigated.[28] Lewis *et al.* performed a diverse range of reactions on bromo-arene diol **IV-13**, demonstrating its versatility as a chiral starting material. After converting arene diol **IV-13** to its acetonide protected methyl ester **IV-15**, dihydroxylation was conducted to give diol **IV-16** (scheme IV-07). Additionally, Lewis and co-workers conducted the Diels–Alder reaction of diene **IV-15** with PTAD yielding cycloadduct **IV-17,** as well as synthesising iron complexes **IV-18** and **IV-19** through treatment of **IV-15** with nonacarbonyldiiron and (scheme IV-07). It should be noted that the reactivity of bromo-diene **IV-15** with nonacarbonyldiiron is distinct for that when reacting the analogous non-brominated diene with nonacarbonyl-diiron.[31]



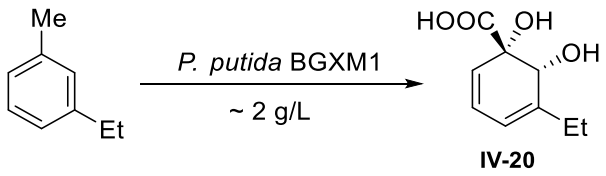
Scheme IV-07: Synthesis of a range of enantiopure brominated compounds from bromo-arene diol **IV-13**.[28] *a*) TMS-CHN_2, MeOH, benzene, RT. *b*) *p*TSA, 2,2-DMP, RT. *c*) OsO_4, NMO, acetone, H_2O, RT. *d*) PTAD, acetone, RT. *e*) $Fe_2(CO)_9$, THF, RT.

Lewis *et al.* have also investigated the use of bromo-arene diol derived diene **IV-13** in cross coupling reactions (scheme IV-08). They showed that a variety of groups could be incorporated at C3 using this cross-coupling approach, infinitely multiplying the number of compounds accessible through the microbial oxidation of 3-bromobenzoic acid.[28]



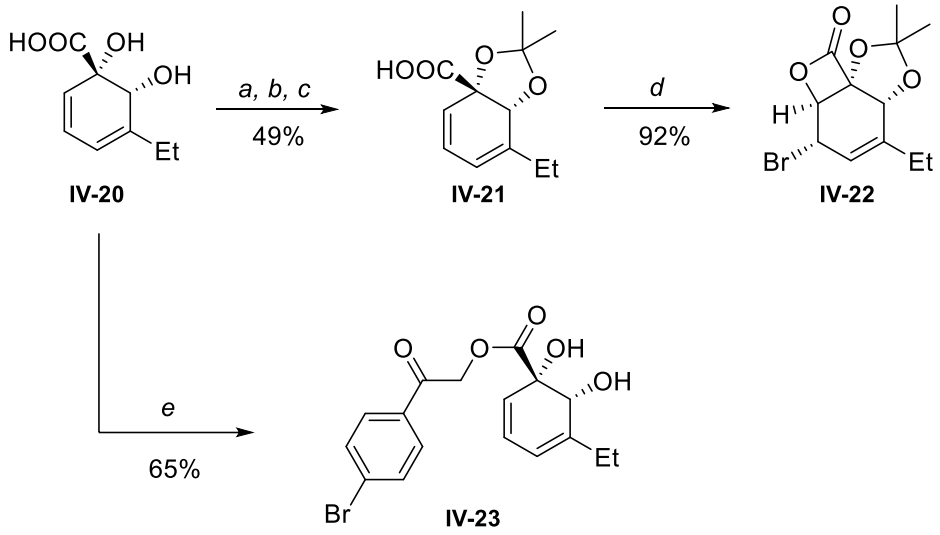
Scheme IV-08: Cross coupling reactions of bromo-arene diol **IV-13**.[28] *a*) *p*-tolylboronic acid, $Pd(PPh_3)_4$, DMF, H_2O, K_2CO_3, RT. *b*) TMS-CHN_2, MeOH, benzene, RT. *c*) (TIPS)acetylene, $Pd(PPh_3)_4$, CuI, $BuNH_2$, THF, RT.

In 2005, Banwell reported the microbial oxidation of 3-ethyltoluene to ethyl-arene diol **IV-20**.[29] The organism used in this biotransformation, *Pseudomonas putida* strain BGXM1, was capable of effecting both the oxidation of the methyl group of 3-ethyltoluene to a carboxylic acid, as well as dearomative oxidation to form arene diol **IV-20** (scheme IV-09). Whilst this strategy differs slightly from the microbial oxidation of benzoic acids using BZDO expressing organisms, the good substrate yields obtained using this method make this an equally feasible alternative to such organisms.



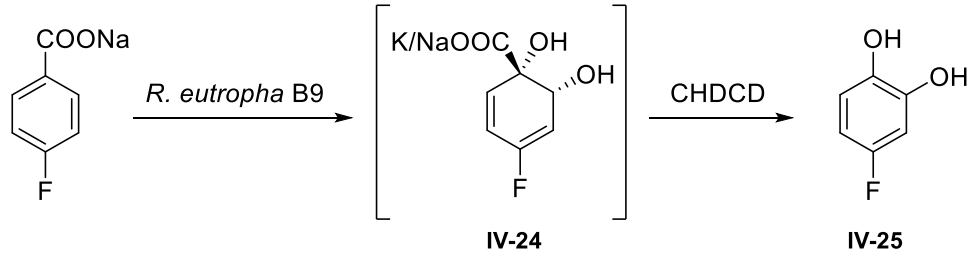
Scheme IV-09: Microbial oxidation of 3-ethyltoluene.[29]

Following their synthesis of ethyl-arene diol **IV-20**, Banwell and co-workers conducted preliminary studies into its uses in synthesis. Lactone **IV-22** was formed through alkene bromination of diene **IV-21** followed by spontaneous intra-molecular attack of the proximal carboxylic acid on the resulting bromonium ion (scheme IV-10). This reaction had been previously reported by Myer's on the non-ethylated analogue of **IV-21**.[32] The alkylation of the carboxylic acid of **IV-20** was also demonstrated to give **IV-23** (scheme IV-10). Lewis' and Banwell's research concludes the synthetic studies into substituted arene *ipso,ortho*-diols, with both examples focussing on arene diols substituted at C3.



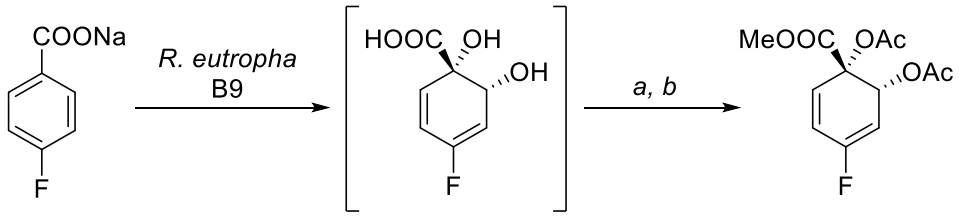
Scheme IV-10: Derivatisation of 3-ethyl-arene diol **IV-20**. *a*) CH_2N_2, CH_2Cl_2, EtOH, 18°C. *b*) *p*TSA, 2,2-DMP, 18°C. *c*) K_2CO_3, MeOH, 18°C. *d*) Br_2, $NaHCO_3$, CH_2Cl_2, 0°C. *e*) α,*p*-dibromoacetophenone, NEt_3, acetone, 18°C.

In 1971, Reiner reported the microbial oxidation of sodium 4-fluorobenzoate using *Ralstonia eutropha* B9 (formerly classified *Alcaligenes eutrophus* B9).[25] The resulting fluoro-arene diol **IV-24** was never isolated by Reiner, and instead the success of the microbial oxidation was based on the formation of fluoro-catechol **IV-25** when reacting an aqueous solution of suspected fluoro-arene diol **IV-24** with 3,5-cyclohexadiene-1,2-diol-1-carboxylic dehydrogenase (CHDCD), an enzyme known to catalyse the formation of catechols from arene *ipso, ortho*-diols (scheme IV-11).



Scheme IV-11: Initial report of the microbial oxidation of sodium 4-fluorobenzoate by Reiner.[25]

The precedent set by Reiner was expanded upon by Reineke in 1978.[26] The isolation and characterisation fluoro-diene **IV-27**, a protected derivative of fluoro-arene diol **IV-26**, was achieved, which was found to possess greater stability than **IV-26**. Similarly to Reiner's research, the fluoro-arene diol was never isolated by Reineke. Instead, following the extraction of acid **IV-26** from the biotransformation supernatant with EtOAc, the organic solution of acid **IV-26** was methylated using diazomethane and subsequently stirred with pyridine and acetic anhydride to afford fluoro-diene **IV-27** (scheme IV-12).

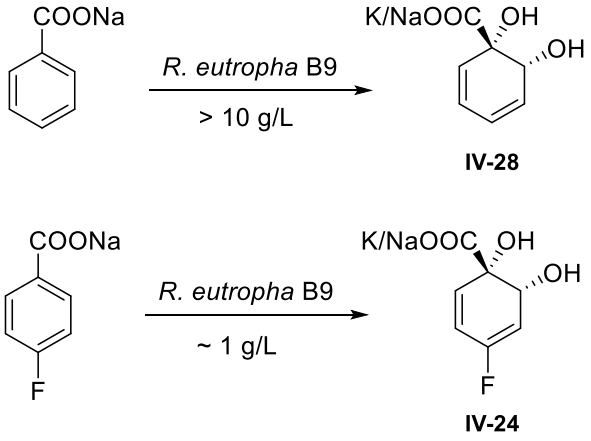


Scheme IV-12: Reineke's synthesis of fluoro-diene **IV-27**. *a*) CH_2N_2, EtOAc, RT. *b*) Ac_2O, pyridine, RT. Yields not quantifiable.

Since Reineke's research, there has been a lack of synthetic chemistry conducted in this field. We envisaged that, through isolation of fluoro-arene diol **IV-24** and subsequent derivatisation, a wide range of novel, fluorinated compounds could be easily accessed in synthetically useful quantities. In addition, vital information on the reactivity of fluoro-dienes could be ascertained. Information gained in this regard may be of importance in the synthesis of biologically or chemically useful compounds.

Results and discussion

Conditions for the microbial dearomatisation of sodium benzoate are widely reported in the literature and are now well established.[32-34] After growing a culture of *R. eutropha* B9 cells in Hutner's mineral base, sodium benzoate and D-fructose are fed to the aerated culture continuously over several days. Conversion of sodium benzoate to arene diol **IV-28** can be monitored either by HPLC or by the concentration of oxygen in the fermentation broth. Typically, the quantity of arene diol obtained is >10 g/L of culture (scheme IV-13). When conducting the microbial dearomatisation of sodium 4-fluorobenzoate, it was discovered that only minor changes to the reported procedures were required to furnish fluoro-arene diol **IV-24** in reasonable quantities (scheme IV-14).[35]



Scheme IV-13: Microbial arene oxidation of sodium benzoates using *Ralstonia eutropha* B9.

During the fermentation, the consumption of sodium 4-fluorobenzoate was monitored using ^{19}F NMR (figure IV-02, chemical shifts for sodium 4-fluorobenzaote and product **IV-24** were observed to drift slightly between each assay, with the resonance for sodium 4-fluorobenzoate being observed between δ –117.7 and –116.7 ppm, whereas the resonance for **IV-24** was observed between δ –122.9 and –123.8 ppm).[35] Using ^{19}F NMR, it was judged that dearomative oxidation of sodium 4-fluorobenzoate proceeds at a significantly slower rate than sodium benzoate, resulting in the quantity of fluoro-arene diol **IV-24** obtained from the biotransformation being ~1 g/L. This observed difference in reactivity is consistent with the work of Lipscomb *et al*., who reported the relatively slow dearomative oxidation of sodium fluorobenzoates in single turnover experiments with BZDO and BZDR enzyme extracts.[30] Lipscomb determined that the observed difference in reactivity was not a consequence of poorer substrate binding in the enzyme active site. An alternative proposed explanation for the slower dearomative oxidation of sodium 4-fluorobenzoate could be the decreased electron density at C2 disfavouring biocatalytic oxidation, however this hypothesis has not yet been conclusively proven.

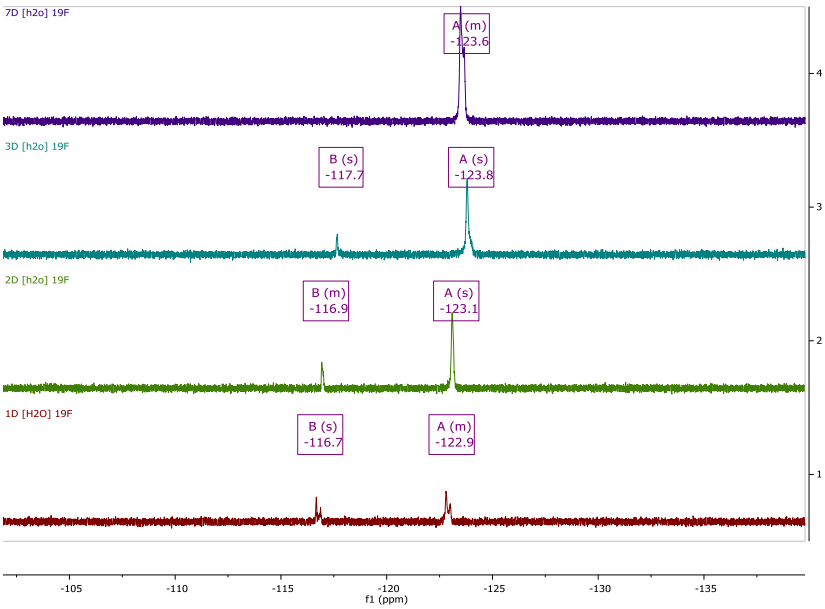
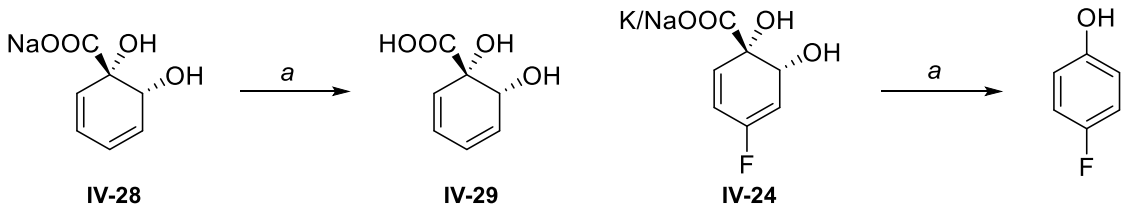


Figure IV-02: ^{19}F NMR spectra of sodium 4-fluorobenzoate fermentation broth after 1 day (red, bottom), 2 days (green), 3 days (turquoise) and 7 days (blue, top).

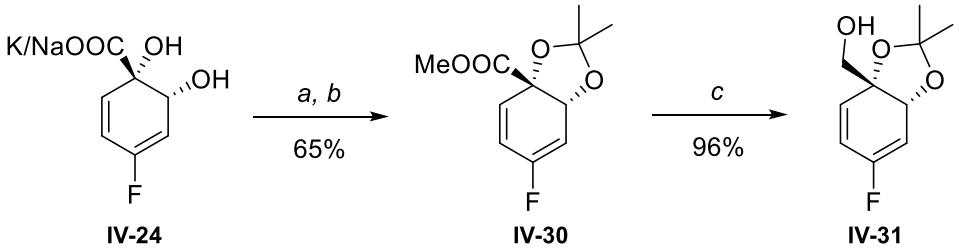
Re-aromatisation of fluoro-arene diol **IV-24** was also found to occur far more readily than the corresponding re-aromatisation of its non-fluorinated analogue **IV-28**.[35] In order to isolate the non-fluorinated free acid **IV-29**, an aqueous solution of carboxylate **IV-28** can be cooled to 0°C and acidified to around pH 3 with conc. HCl. Acid **IV-29** may then be extracted with EtOAc and the solvent removed under vacuum.[32] When attempting to isolate the free acid of fluoro-carboxylate **IV-24**, following this procedure results in complete re-aromatisation of the fluoro-arene diol to give 4-fluoro-phenol (scheme IV-14). This is consistent with what Reineke observed when trying to isolate such fluoro-arene diols in 1978.[26] As such, it was necessary to isolate the product as its mixed sodium/potassium salt **IV-24** prior to derivatisation, which was achieved by adding isopropanol to an aqueous solution of **IV-24**, effecting precipitation of the crude product. This precipitation strategy has previously been used to isolate non-fluorinated arene diol **IV-28**.[33, 36]



Scheme IV-14: Acidification of fluoro-arene diol **IV-24** and its non-fluorinated analogue **IV-28**. *a*) HCl, water, 0°C.

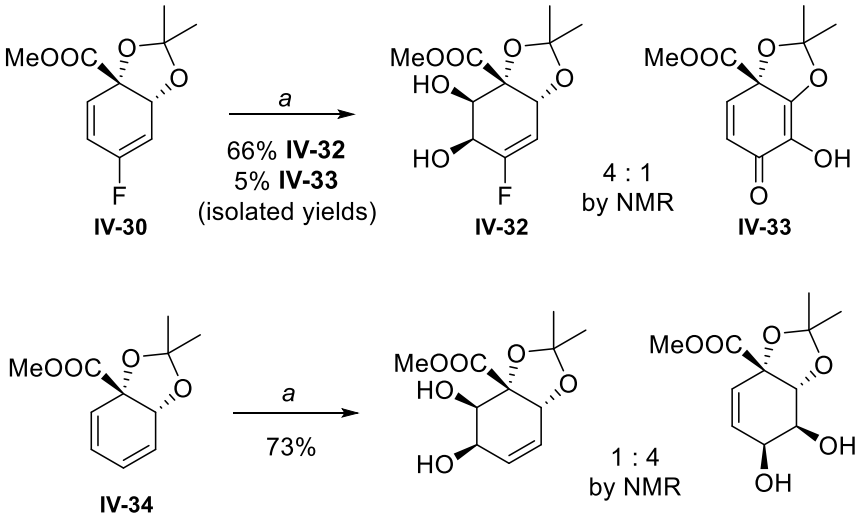
The diol of arene diol **IV-28** is commonly protected as an acetonide, prior to esterification of the carboxylic acid to a methyl ester. The resulting compound has been used as a starting material in the

synthesis of multiple enantiopure compounds.[32, 37-39] Fluoro-arene diol **IV-24** was therefore derivatised as its acetonide protected methyl ester (scheme IV-15),[35] which was then elaborated oxidatively to yield various novel, enantiopure compounds. Additionally, it was found that methyl ester **IV-30** could be reduced to primary alcohol **IV-31** (scheme IV-15), however synthetic research based on this compound is ongoing.



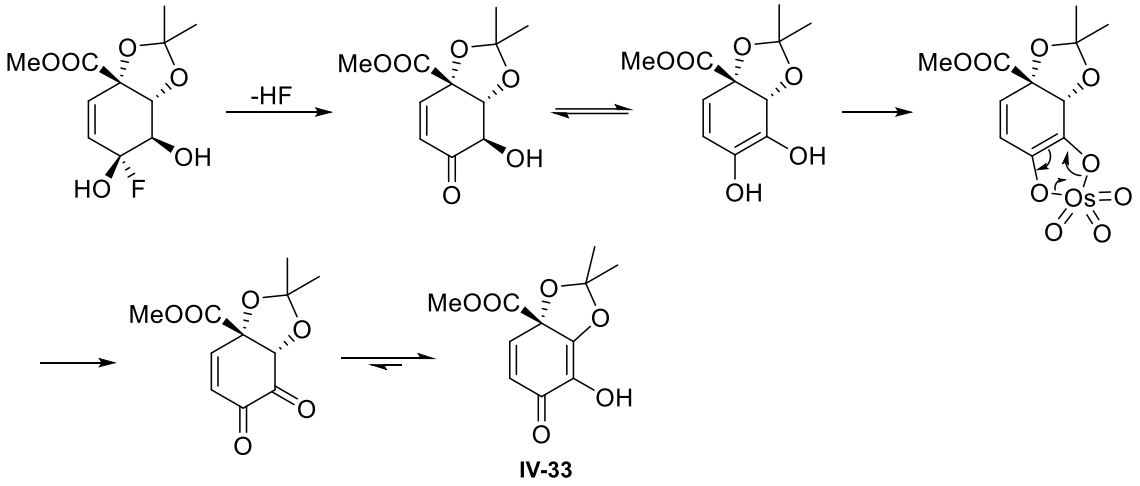
Scheme IV-15: Acetonide protection and esterification of arene diol **IV-24**. *a*) Trifluoroacetic acid (5.0 equiv.), 2,2-dimethoxypropane, acetone, 0°C to RT, 16 hours. *b*) TMS-diazomethane, MeOH, benzene, RT, 20 minutes. *c*) $LiBH_4$ (2.0 equiv.), THF, 0°C to RT, 16 hours.

Fluoro-diene **IV-30** was dihydroxylated using OsO_4, which gave a mixture of 2 products: **IV-32** and **IV-33** (scheme IV-16).[35] Dihydroxylation of the non-fluorinated alkene of diene **IV-30** seemingly proceeded at a significantly faster rate than dihydroxylation of the fluorinated alkene, resulting in **IV-32** as the major product. Interestingly, dihydroxylation of the analogous non-fluorinated diene **IV-34** shows the exact opposite regioselectivity (scheme IV-16),[40] which suggests that the electronics of the diene are significantly affected by the introduction of fluorine at C4. The preference for dihydroxylation at the non-fluorinated alkene is in agreement with Boyd's research on the dihydroxylation of fluoro-dienes derived from fluoro-arene *ortho,meta*-diols.[22, 23]



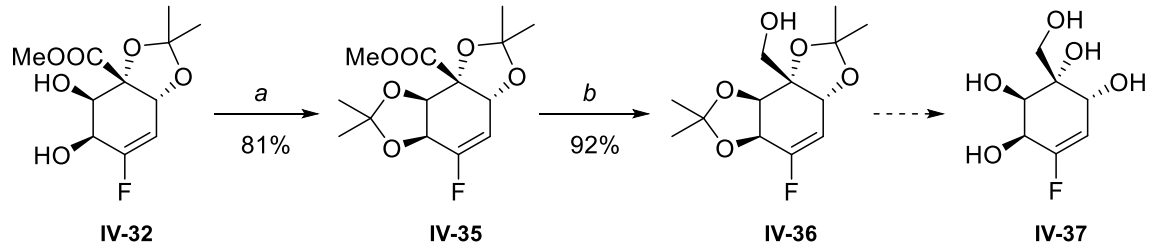
Scheme IV-16: Dihydroxylation of fluoro-diene **IV-30** compared to reported dihydroxylation of non-fluorinated diene **IV-34**.[40] *a*) OsO_4 (2.5 wt% in *t*BuOH, 5 mol%), NMO (1.3 equiv.), acetone, water, RT, 16 hours.

Boyd did not report, however, the formation of a product resulting from the dihydroxylation of the fluoro-alkene. In the present case, elimination of fluoride from the regioisomeric diol of **IV-32** occurs, and subsequent oxidation of the resulting α-hydroxy ketone then ensues (Scheme IV-17). This unwanted side reaction gives dienone **IV-33** as a minor product. It should be noted that the discrepancy between the isolated yield of dienone **IV-33** and the observed ratio of diol **IV-32** to dienone **IV-33** by NMR is likely a result of its low stability. Dihydroxylations of fluoro-alkenes have been reported previously, with elimination of fluoride also occurring on these occasions.[5, 41]



Scheme IV-17: Proposed intermediates for the formation of diene-one **IV-33**.

Cyclitols in general are known to possess a rich variety of biological functions,[20, 21, 42] whilst the introduction of fluorine into cyclitols is thought to prevent metabolic degradation and increase lipophilicity.[43] The synthesis of fluoro-cycitols, however, is known to be arduous. Consequentially, fluoro-cyclitol **IV-37** was selected as a synthetic target. Protection of diol **IV-32** as an acetonide and reduction of the methyl ester furnished primary alcohol **IV-36**, a protected fluoro-cyclitol (scheme IV-18).[35] Deprotection of (bis)acetonide **IV-36** has been successfully conducted by refluxing a solution of **IV-36** in TFA and MeOH, as evidenced by ^{1}H NMR of the crude product (figure IV-03), however successful purification of the resulting fluoro-cyclitol **IV-37** has not yet been achieved.



Scheme IV-18: Attempted synthesis of fluoro-cyclitol precursor **IV-37**. *a*) *p*TSA (13 mol%), 2,2-dimethoxypropane, acetone, RT, 48 hours. *b*) $LiBH_4$ (2.0 equiv.), THF, 0°C to RT, 16 hours.

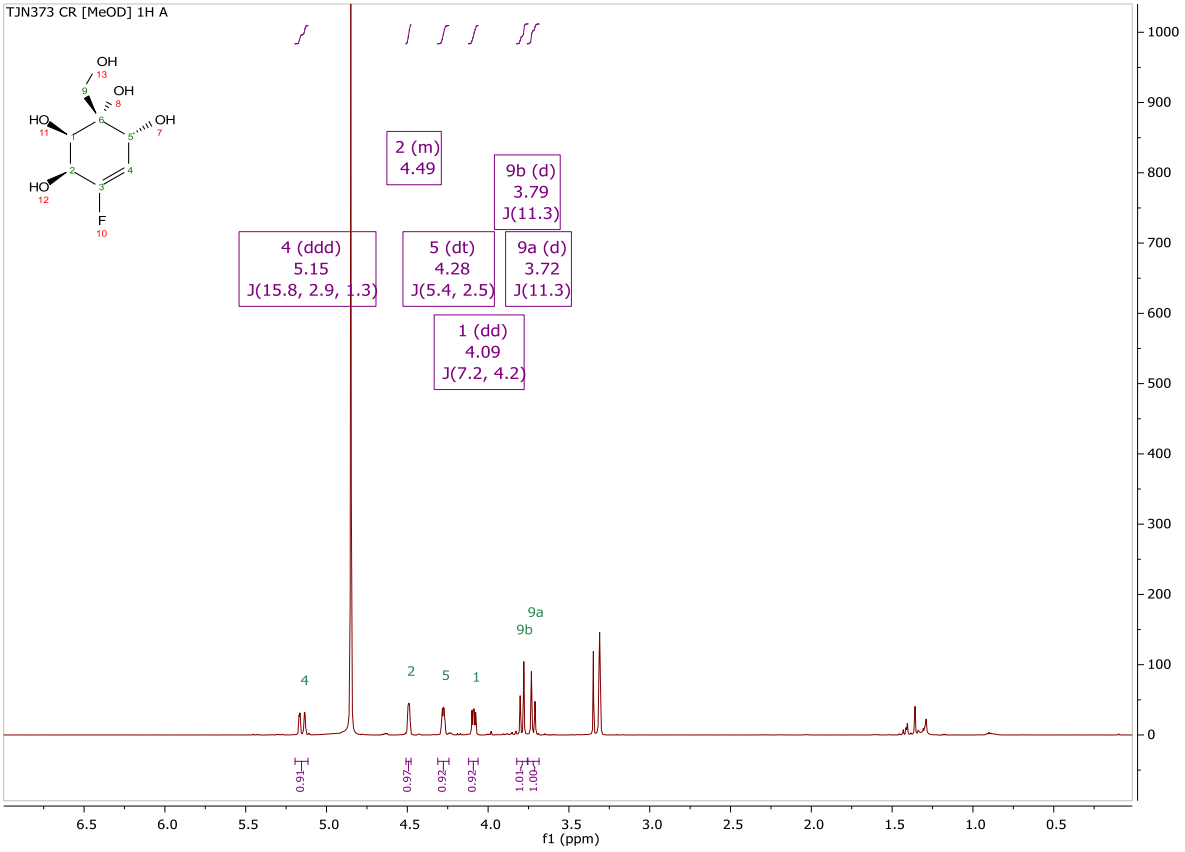
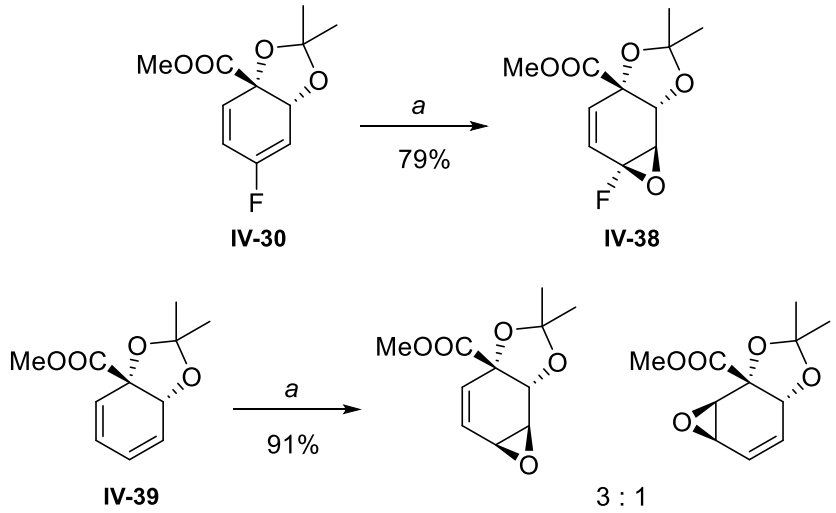


Figure IV-03: Crude ^{1}H NMR spectrum of fluoro-cyclitol **IV-37**.

In 1990, Carless reported the epoxidation of a fluoro-arene *ortho,meta*-diol derived fluoro-diene.[18] This reaction yielded 2 products, with the relative ratios of each product unreported. Contrary to Carless' findings, mono-epoxidation of fluoro-diene **IV-30** gave fluoro-epoxide **IV-38** exclusively.[35] Furthermore, epoxidation of the analogous non-fluorinated diene **IV-39** has been shown to give a mixture of regioisomers (scheme IV-19).[32] This unique selectivity may be a result of hydrogen bonding between the fluorine and *m*CPBA, thus directing epoxidation to the fluoro-alkene.

The reported regio-selectivity of fluoro-epoxide **IV-38** has been assigned based on analysis of its ^{1}H and ^{13}C NMR spectra (figure IV-04). J values for the alkene carbon doublets 131.6 and 123.5 are 12.9 and 41.1 Hz respectively. In contrast to this, J values for epoxide carbon doublets 89.9 and 53.6 are 261.9 and 17.6 Hz respectively. These J values are consistent with the fluoro-alkene being epoxidized, confirming the stated regio-selectivity. The stereo-chemistry of **IV-38** was initially assigned based on the reported stereo-selectivity when epoxidizing the analogous non-fluorinated compound.[32] This was conclusively confirmed by obtaining an X-ray crystal structure of a derivative of fluoro-epoxide **IV-38** (figure IV-06, page 156).



Scheme IV-19: Epoxidation of fluoro-diene **IV-30** compared to non-fluorinated diene **IV-39**.[32] *a*) *m*CPBA (1.3 equiv.), CH_2Cl_2, RT, 16 hours.

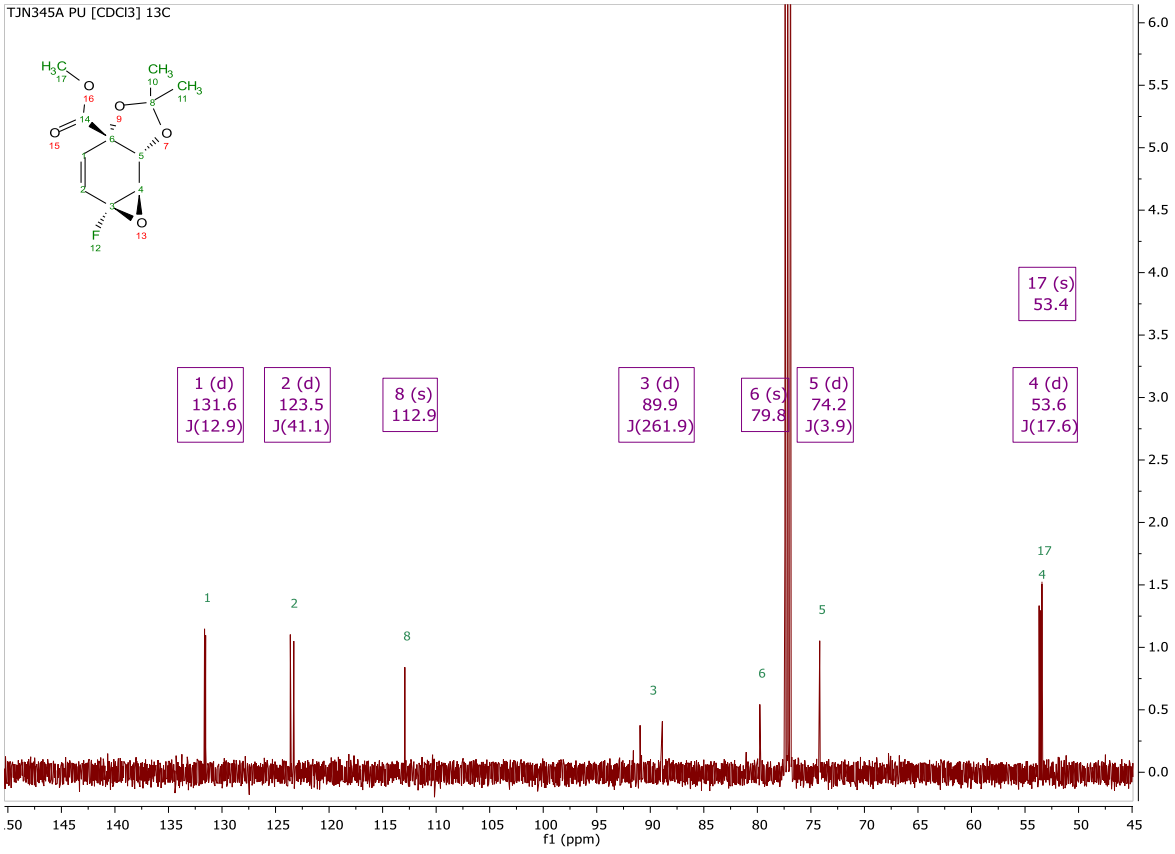
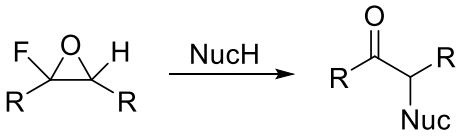


Figure IV-04: Segment of the ^{13}C NMR spectrum of fluoro-epoxide **IV-38**.

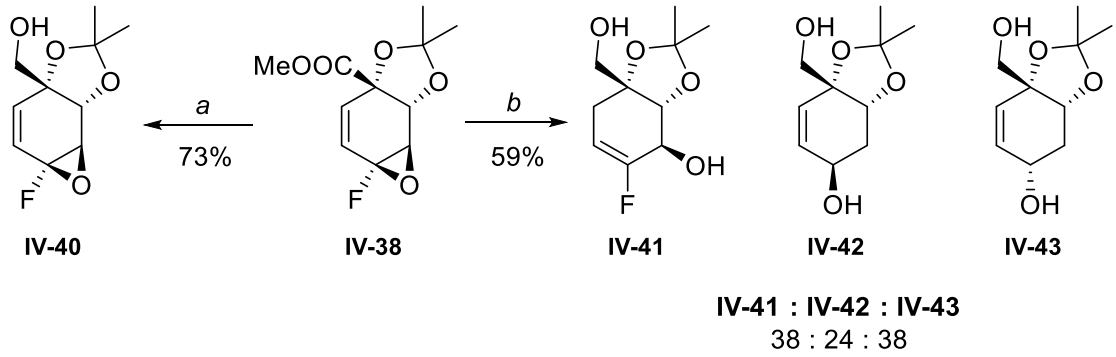
Currently, there are few examples of ring opening reactions on fluoro-epoxides in the literature. Reported reactions tend to focus on ring opening using either a halogen, water or an alcohol as nucleophiles, with ring opening occurring at the non-fluorinated carbon of the epoxide.[44, 45] This leads to elimination of fluoride to form α-substituted ketones (scheme IV-20). Research into the ring

opening reactions of allylic fluoro-epoxides, however, has not yet been conducted, possibly due to difficulty in their preparation.



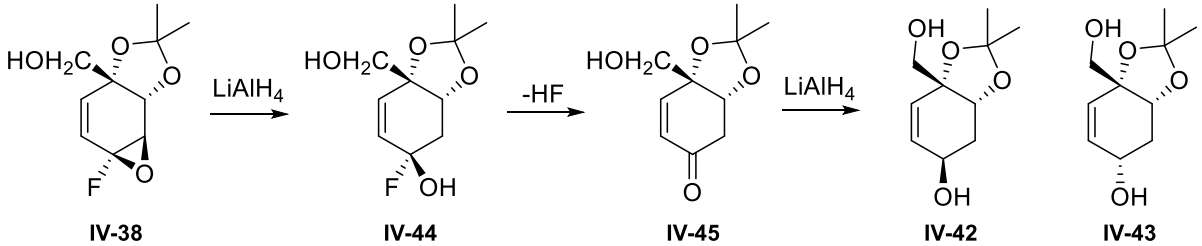
Scheme IV-20: General selectivity observed when reacting fluoro-epoxides with nucleophiles.[44, 45]

Reacting epoxide **IV-38** with $LiBH_4$ resulted in the reduction of the methyl ester to give primary alcohol **IV-40**, whereas reaction with $LiAlH_4$ resulted in epoxide ring opening in addition to methyl ester reduction (scheme IV-21). Allylic epoxide opening of fluoro-epoxide **IV-38** yielded fluoro-alkene **IV-41**. Compounds **IV-42** and **IV-43** are a result of epoxide ring opening from nucleophilic attack of $LiAlH_4$ at the non-fluorinated epoxide carbon. It is noteworthy that epoxide ring opening at the highly sterically encumbered non-fluorinated epoxide carbon predominates over ring opening at the less sterically encumbered fluorinated epoxide carbon.



Scheme IV-21: Reactions of epoxide **IV-38** with $LiBH_4$ and $LiAlH_4$. *a*) $LiBH_4$ (2.1 equiv.), THF, 0°C to RT, 24 hours. *b*) $LiAlH_4$ (3.2 equiv.), Et_2O, 0°C to RT, 16 hours.

A proposed mechanism for formation of products allylic alcohols **IV-42** and **IV-43** commences with epoxide opening at the non-fluorinated epoxide carbon of **IV-38** giving α-fluoro-alcohol **IV-44**, which rapidly eliminates fluoride to give enone **IV-45** (scheme IV-22). Non-diastereoselective 1,2-reduction of the resulting enone then provides a diastereo-isomeric mixture of allylic diols **IV-42** and **IV-43** (scheme IV-22).



Scheme IV-22: Proposed intermediates in the formation of allylic alcohols **IV-42** and **IV-43**.

The stereochemistry of allylic alcohols **IV-42** and **IV-43** could be assigned using ^{1}H NMR. Since the Karplus equation shows that the strength of coupling between vicinal protons is dependent on their dihedral angle,[46] J values in the ^{1}H NMR spectra of **IV-42** and **IV-43** could be used for this purpose.

Analysis of the 3D structure of diastereomer **IV-43** shows that the dihedral angles between H^{3} and each H^{4} proton are significantly different. Indeed, the ^{1}H NMR spectrum of **IV-43** shows that H^{3} couples with protons H^{4A} and H^{4B} to different extents, resulting in respective J values of 5.5 and 10.0 Hz (figure IV-05). These differing J values are consistent with what is predicted for **IV-43** based on the Karplus equation, allowing the stereochemistry of this compound to be assigned.

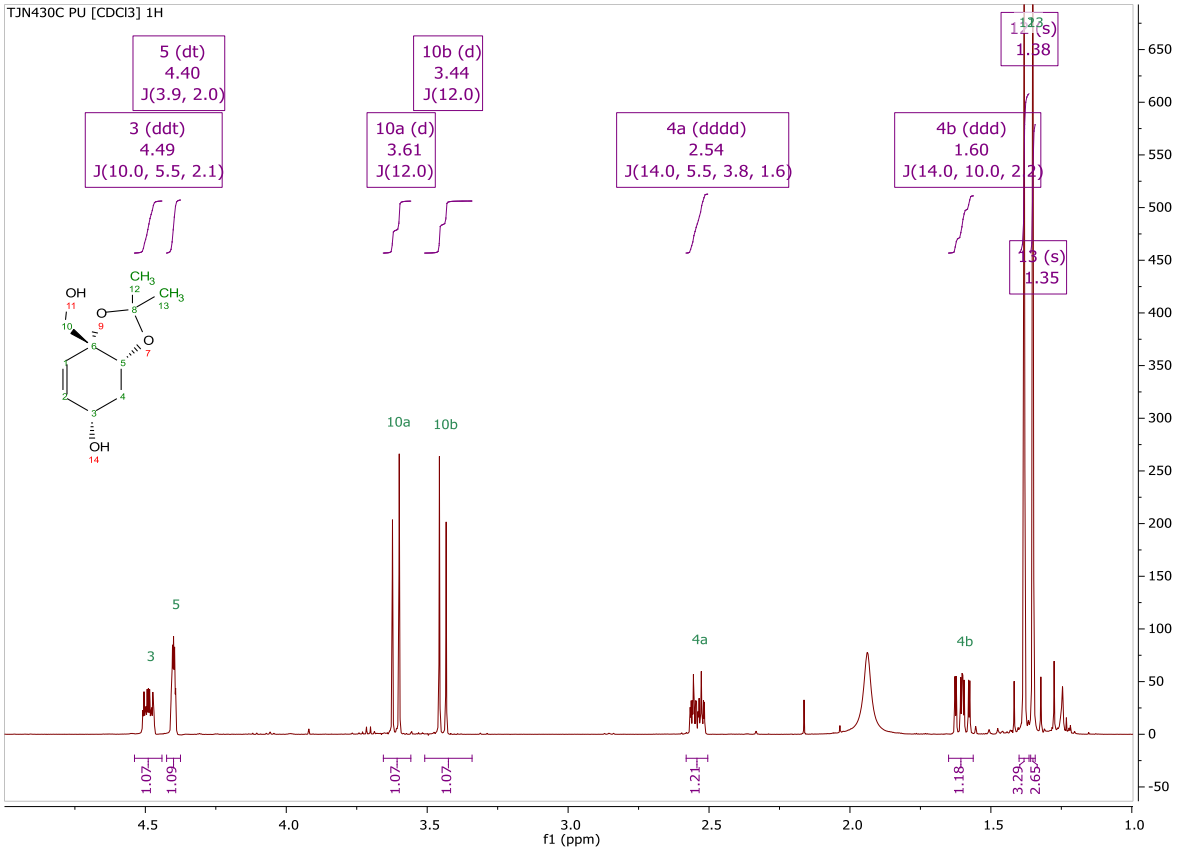


Figure IV-05: Segment of the ^{1}H NMR spectrum of **IV-43**.

In contrast, the 3D structure of **IV-42** shows the dihedral angle between H^{3} and both H^{4} to be similar, which should result in similar J values between each. Whilst the splitting pattern of proton H^{3} cannot be unambiguously assigned – meaning J values for H^{3} cannot be calculated – the splitting patterns of both H^{4} protons suggest that this is the case. The J values resulting from coupling with H^{3} are seemingly 3.5 Hz and 4.7 Hz for H^{4a} and H^{4b} respectively (figure IV-06), once more corroborating what was predicted base on the Karplus equation.[46]

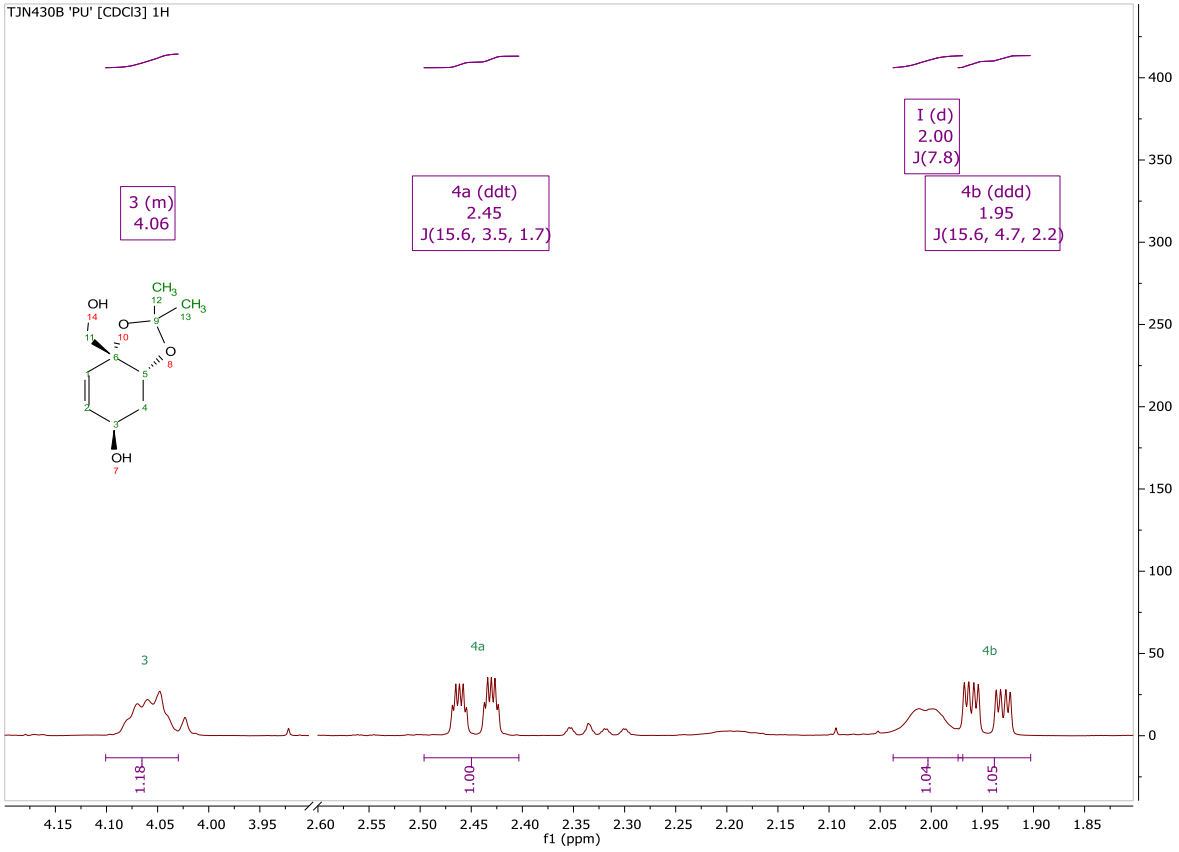
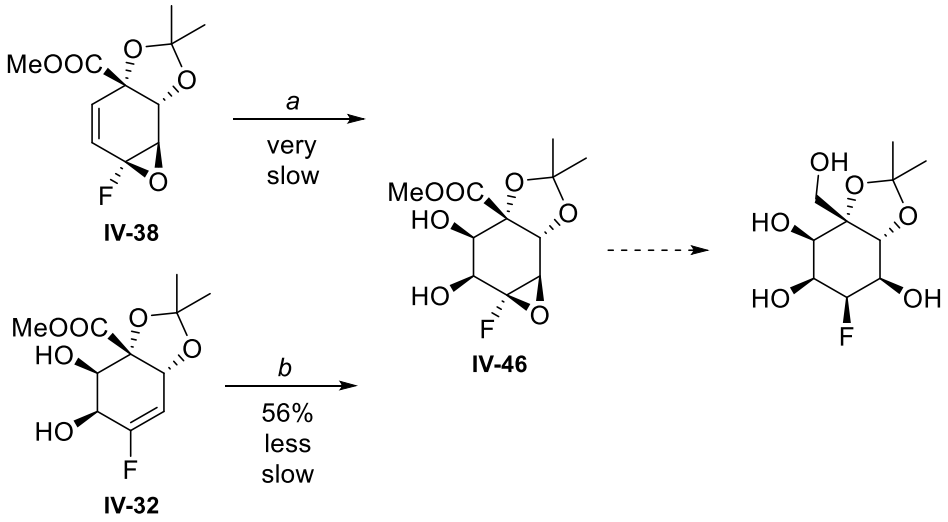


Figure IV-06: Segment of ^{1}H NMR spectrum of diastereomer **II-42**.

Dihydroxylation of fluoro-epoxide **IV-38** has been attempted using OsO_4, however this reaction was found to proceed at an extremely slow rate, forming only a small quantity of product after 3 days. As such, the epoxidation of diol **IV-32** was instead pursued, which proceeded at a more acceptable rate, to furnish fluoro-epoxide **IV-46** (scheme IV-23). Comparison of the crude ^{1}H NMR spectra of the product obtained through each method showed that the same diastereomer was formed in both instances. It was originally envisaged that treating fluoro-epoxide **IV-46** with $LiAlH_4$ could aid in the synthesis of a saturated fluoro-cyclitol, however, based on our previous observations in the reaction of fluoro-epoxide **IV-38** with $LiAlH_4$, this synthetic sequence was not attempted. The synthesis of saturated fluoro-cyclitols is ongoing.



Scheme IV-23: Synthesis of poly-hydroxylated fluoro-epoxide **IV-46**. *a*) OsO_4 (2.5 wt% in *t*BuOH, 5 mol%), NMO (1.3 equiv.), acetone, water, RT, 3 days. *b*) *m*CPBA (3.0 equiv.), CH_2Cl_2, RT, 5 days.

Despite fluoro-epoxide **IV-46** not finding use in the synthesis of saturated fluoro-cyclitols, it was possible to obtain the crystal structure of **IV-46** through X-ray diffraction (figure IV-06). This allowed the confirmation of the stereo-chemistry of both fluoro-epoxide **IV-38**, diol **IV-32** and dehydroxylated epoxide **IV-46**.

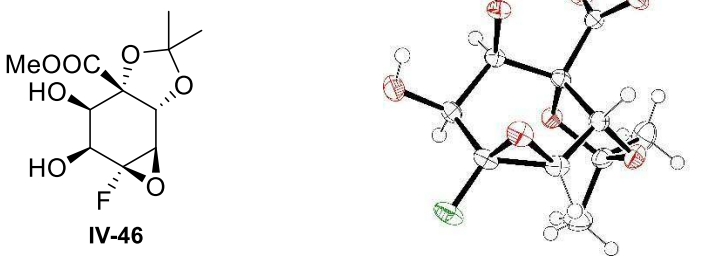
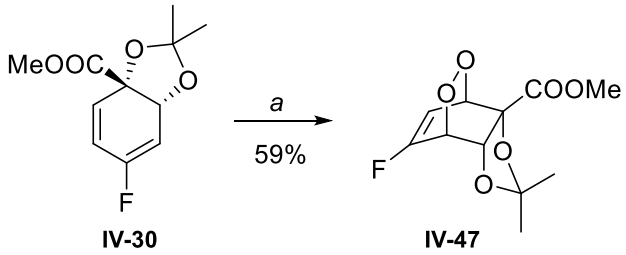


Figure IV-06: Crystal structure of fluoro-epoxide **IV-46**.

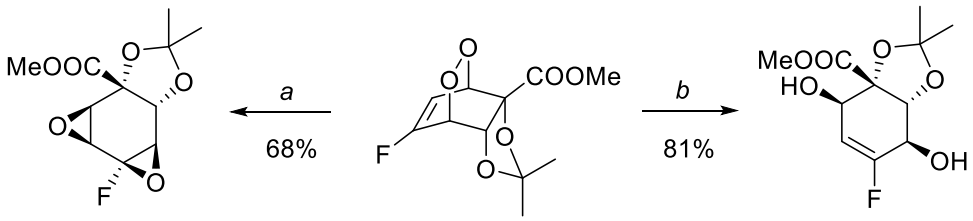
Singlet oxygen cycloadditions are an established methodology for the incorporation of oxygen into carbon frameworks bearing dienes. Utilising this reactivity, Lewis *et al.* reported the synthesis of a range of highly oxygenated compounds from non-fluorinated arene diol **IV-28** in 2012 and 2014.[47, 48] Singlet oxygen cycloadditions on fluoro-dienes, however, have not been reported to date, and could allow access to an array of highly oxygenated, fluorine containing compounds. As such, endoperoxide **IV-47** was synthesised from fluoro-diene **IV-30** (scheme IV-24). Both *Methylene Blue* and TPP were tested as photosensitisers for this transformation, however TPP was found to give endoperoxide **IV-47** in the greater yield.



IV-30 **IV-47**

Scheme IV-24: Cycloaddition of singlet oxygen to fluoro-arene diol **IV-30**. *a*) TPP, O_2, *hv*, CH_2Cl_2, 0°C, 12 hours.

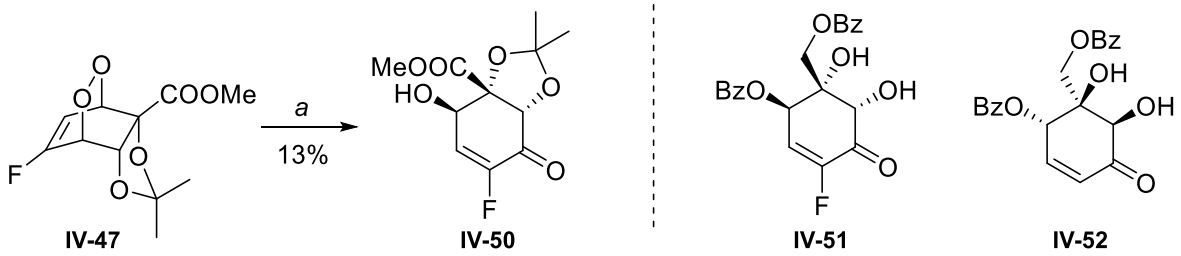
Treating endoperoxide **IV-47** with Co(TPP) results in a facile isomerisation reaction affording (bis)epoxide **IV-48**, whereas reductive cleavage of endoperoxide **IV-47** was achieved using thiourea to give diol **IV-49** (scheme IV-25). Both these transformations proceeded as predicted by previous experiments conducted on the analogous non-fluorinated compound.[48] Diol **IV-49** is of interest as it could be used in the synthesis of a fluoro-cyclitol, whereas investigation into the epoxide ring opening reactivity of (bis)epoxide **IV-48** may provide insight into the reactivity differences between fluorinated and non-fluorinated epoxides.



IV-48 **IV-47** **IV-49**

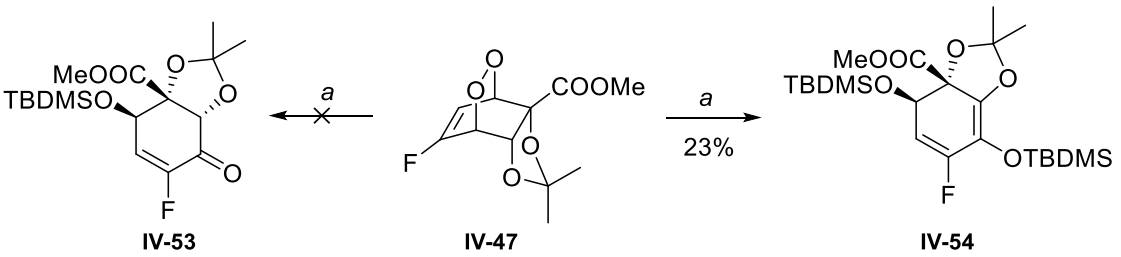
Scheme IV-25: Derivatisation of endo-peroxide **IV-47**. *a*) Co(TPP), CH_2Cl_2, RT, 16 hours. *b*) Thiourea (1.1 equiv.), CH_2Cl_2, MeOH, RT, 16 hours.

The Kornblum–Delamare rearrangement can provide access to γ-hydroxyenones from endoperoxides. Through reacting fluoro-endoperoxide **IV-47** with DIPEA, α-fluoro-γ-hydroxy-enone **IV-50** was synthesised (scheme IV-26). Low yields were observed for this reaction, which is likely a result of the low stability of γ-hydroxyenone **IV-50**. This is consistent with the observations made by Lewis *et al.* when synthesising similar, non-fluorinated γ-hydoxyenones.[47] The tendency of the γ-hydroxyenone motif to undergo side reactions was also noted by Spivey, who found γ-hydroxyenones to undergo a dimerization reaction through an oxy-Michael addition.[49] Through its use as an alkene in Diels–Alder reactions or in conjugate additions, this highly functional motif could be of utility in gaining access to an immense range of novel, enantiopure compounds. Furthermore, due to the reported biological activity of (–)-zeylenones and related compounds,[50, 51] it may be of interest to synthesise (+)-fluoro-zeylenone **IV-51** using similar chemistry.



Scheme IV-26: Synthesis of 4-hydroxy-2-fluoro-enone **IV-50** (left). Potential target compound (+)-fluoro-zeylenone **IV-51** and natural product (–)-zeylenone **IV-52** (right).[50] *a*) DIPEA, CH_2Cl_2, RT, 20 hours.

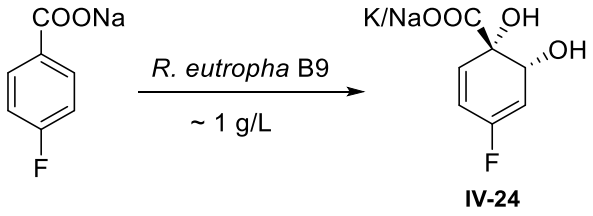
In order to circumvent undesired side reactions of γ-hydroxy-enone **IV-50**, protection of its secondary alcohol was attempted. Interestingly however, trying to affect the one-pot Kornblum–Delamare and subsequent silyl protection of fluoro-endoperoxide **IV-47** resulted not in the formation of **IV-53**, but instead the formation of fluoro-diene **IV-54** (scheme IV-27). Similarly to the formation of γ-hydroxyenone **IV-50**, the yield of this reaction was also less than optimal; this may also be attributed to the low stability of **IV-50**, which is a likely intermediate in the formation of fluoro-diene **IV-54**. Similar dienes have been reported to undergo cycloaddition reactions with, for example, singlet oxygen or mono-substituted alkynes.[52, 53]



Scheme IV-27: Derivatisation of endoperoxide **IV-47**. *a*) NEt_3 (3.6 equiv.), TBDMSOTf (1.3 equiv.), DMAP, CH_2Cl_2, 0°C to RT, 16 hours.

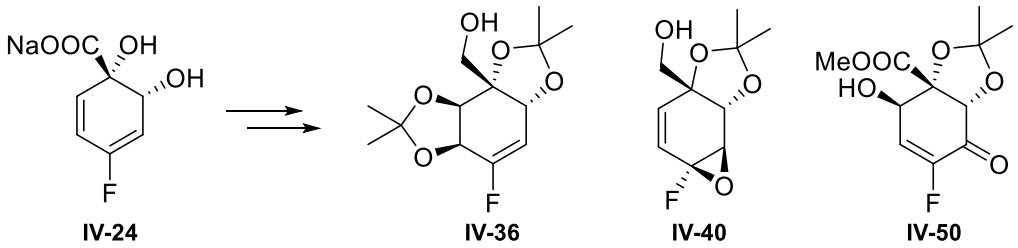
Conclusions and future work

The synthesis of cyclic fluoro-alkenes is a non-trivial pursuit; however, it has been demonstrated that, through microbial oxidation, enantiopure fluoro-dienes can be synthesised from sodium 4-fluorobenzoate in synthetically useful quantities (scheme IV-28). This microbial oxidation can be achieved using *Ralstonia eutropha* B9 and conversion of substrate into the desired arene diol can be followed by ^{19}F NMR.



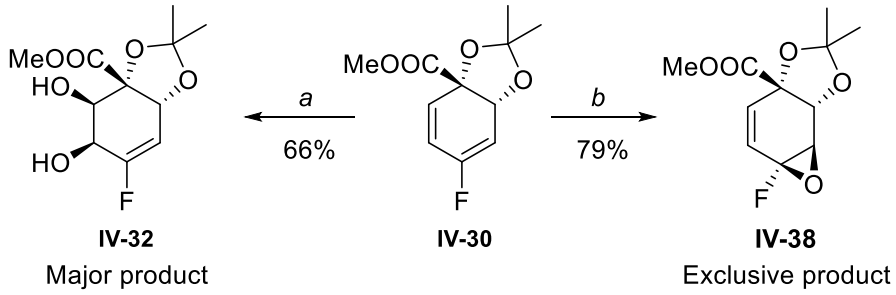
Scheme IV-28: Microbial arene oxidation of sodium 4-fluorobenzoate to fluoro-arene diol **IV-24**.

Various oxidative transformations have been conducted on fluoro-arene diol **IV-24**, resulting in an array of novel, highly oxygenated fluoro-carbocycles being synthesised, including fluoro-cyclitol precursor **IV-36**, fluoro-epoxide **IV-40** and α-fluoro-γ-hydroxyenone **IV-50** (scheme IV-29). The synthesised compounds could be further functionalised in numerous number of ways. This essential research lays the foundations for further work on fluoro-arene diols, paving the way to the synthesis of more complex or biologically active fluoro-carbocycles.



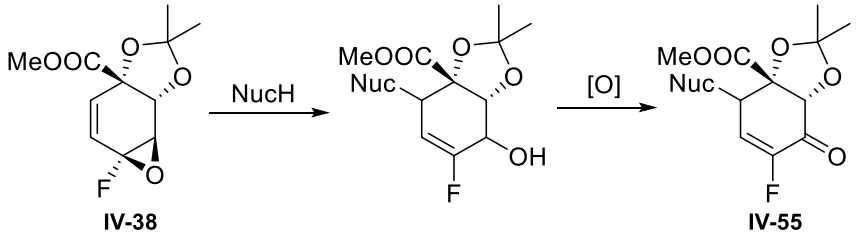
Scheme IV-29: Syntheses of a selection of highly oxygenated compounds from fluoro-arene diol **IV-24**.

Whilst researching the syntheses of these compounds, the unique reactivity of fluoro-alkenes and fluoro-epoxides was also investigated, which has added to the known chemistry of these motifs. Of particular interest is the difference in regioselectivity of epoxidation versus dihydroxylation of fluoro-diene **IV-30** (scheme IV-30), and the regioselectivity of epoxide ring opening reactions of fluoro-allylic epoxide **IV-38**.



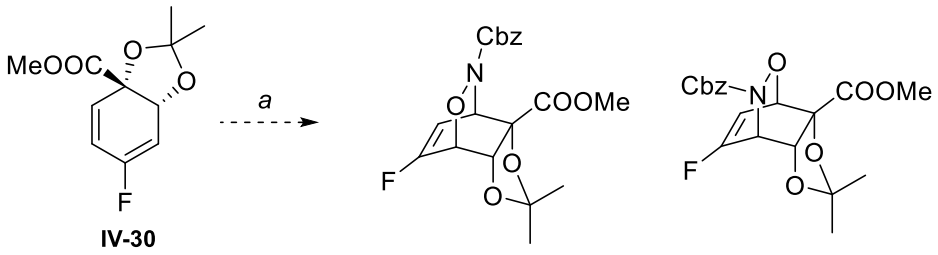
Scheme IV-30: Dihydroxylation and epoxidation of fluoro-diene **IV-30**. *a*) OsO_4, NMO, acetone, water, RT. *b*) *m*CPBA, CH_2Cl_2, RT.

Despite the previously detailed research into oxidative reactions on fluoro-arene diols, a wide expanse of synthetic chemistry relating to fluoro-arene diols remains unexplored. Having already reported the partial allylic epoxide opening of fluoro-epoxide **IV-38** with $LiAlH_4$, it would be of interest to explore whether exclusive allylic epoxide opening of the fluoro-epoxide **IV-38** could be achieved with "softer" nucleophiles. Following this, oxidation of the allylic alcohol to α-fluoro-enone **IV-55** be desirable to allow for further functionalisation (scheme IV-31). Achieving this would not only allow the control of functionality at C6, but also allow further functionalisation of the fluoro-enone.



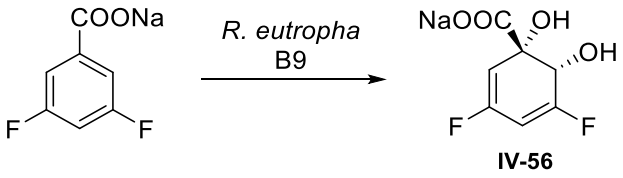
Scheme IV-31: Proposed allylic ring opening of **IV-38** with a soft nucleophile, followed by oxidation of the resulting allylic alcohol to α-fluoro-enone **IV-55**.

Due to the potential biological applications of fluoro-cyclitols,[20, 21, 42, 43] the synthesis of fluoro-cyclitols from arene diol **IV-24** should be brought to a conclusion. In addition to fluoro-cyclitols, it may also be desirable to synthesise aminofluoro-cyclitols using previously established cycloaddition chemistry to install an amine onto the carbocyclic scaffold (scheme IV-32).[54]



Scheme IV-32: Proposed cyclo-addition of fluoro-diene **IV-30**, using conditions developed by Lewis.[54] *a*) Benzyl hydroxycarbamate, $Bu_4N.NaIO_4$, CH_2Cl_2, -78°C.

In addition to continued synthetic chemistry research on sodium 4-fluorobenzoate derived fluoro-arene diols, microbial oxidations of alternative sodium fluorobenzoates should also be investigated. Sodium 3,5-difluorobenzoate was microbially dearomatised by Ribbons *et al.* in 1987 (scheme IV-33),[27] however, following isolation of the product as its methyl ester, the synthetic chemistry of the product was not investigated. Of particular interest would be the use of fluoro-dienes – derived from fluoro-arene diol **IV-56** – in cyclo-additions. This could provide access to enantiopure compounds bearing tetra-substituted, fluoro-carbons. Such compounds would, otherwise, be extremely challenging to synthesise.

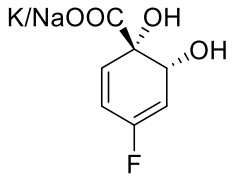


Scheme IV-33: Dearomative dihydroxylation of sodium 3,5-difluorobenzoate.

The previously documented research describes synthetic sequences which allow the synthesis of enantiopure, poly-oxygenated fluoro-carbocycles. This work constitutes the first example of fluoro-arene diol **IV-24** being used in synthesis. Whilst oxidative chemistry of fluoro-arene diol **IV-24** has begun to be explored, continued research into this field is likely to result in the synthesis of novel fluorinated chirons that may be used in the synthesis of more complex targets.

Experimental

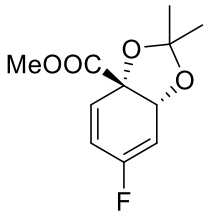
Sodium (1*S*,6*R*)-4-fluoro-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate IV-28



A sterile pipette tip was streaked across a frozen glycerol solution of *Ralstonia eutropha* B9 and added to a sterile solution of Hutner's mineral base (100 mL) and sodium succinate (0.405 g). The solution was placed on an orbital shaker (250 rpm) at 27°C and shaken for 72 h. The resulting cloudy suspension was poured into Hutner's mineral base (1.5 L), which was heated to *ca.* 30°C and through which air was bubbled. Aqueous D-fructose (10 mL, 10% w/v) was then added. A further quantity of D-fructose was added over the following 24 hours via syringe pump. Following this, the culture was induced with sodium 4-fluorobenzoate solution (1.0 M, 5.0 mL) and fed a further quantity of D-fructose (30 mL). ^{19}F NMR showed full conversion of 4-fluorobenzoate to the corresponding *cis*-diol. Repetitive feeding of sodium 4-fluorobenzoate began, with a total of 30 mL of sodium 4-fluorobenzoate being added to the culture over a period of 5 days. The culture was simultaneously fed D-fructose at a rate of 30 mL/24 h.

After full consumption of sodium 4-fluorobenzoate was observed by ^{19}F NMR, the culture was centrifuged (5000 rpm, 45 minutes) and the supernatant collected. The solvent was then removed under vacuum to give a green solid. This solid was found, by ^{1}H NMR, to contain a mixture of the desired product and unconsumed D-fructose. Thus, the material was re-dissolved in water (80 mL), to which isopropanol (800 mL) was added. After 10 min, the cloudy solution was decanted off, leaving behind a brown sludge. A further quantity of water (80 mL) was added to the brown sludge, and isopropanol (800 mL) added. Again, the cloudy solution was decanted off leaving a brown sludge behind. The decanted solutions were cooled to 4°C for 1 h to aid precipitation of the solid. The solid was then filtered off and dried under vacuum to give a cream coloured solid, which contained **IV-28** as the mixed sodium/potassium carboxylate salt and a variable proportion of growth medium salts. 1.35 g of solid was isolated. The product was derivatised as acetonide protected methyl ester **IV-30** before being fully characterised.

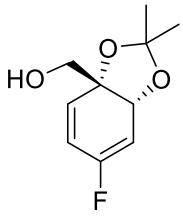
Methyl (3a*S*,7a*R*)-6-fluoro-2,2-dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylate IV-30



To a suspension of *cis*-diol carboxylate **IV-24** (0.287 g, 1.46 mmol, 1.0 equiv.) in 2,2-dimethoxypropane (10 mL) and acetone (1.0 mL), cooled to ~0°C, was added TFA (0.56 mL, 7.32 mmol, 5.0 equiv.) dropwise via syringe pump over 10 minutes. Following addition of TFA, the reaction was allowed to warm to room temperature over 16 hours. The suspension was then filtered through a pad of Celite® and the solution concentrated under vacuum, before being dispersed in H_2O (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent removed to give a dark brown oil. This brown oil was re-suspended in CH_2Cl_2 and the solvent again removed under vacuum to aid excess TFA removal. This was repeated several times. The crude product was re-dissolved in a mixture of MeOH (5.0 mL) and benzene (5.0 mL). TMS-diazomethane (~1.46 mL, apparent 2.0 M solution in hexanes) was added slowly to the resulting solution until a yellow colour persisted and effervescence ceased. After stirring for 20 minutes, the solvent was removed to give a brown oil, which was purified by column chromatography (5% EtOAc, 95% petroleum ether) to give **IV-30** as a colourless oil (0.216 g, 0.947 mmol, 65%).

R_f = 0.28 (10% EtOAc, 90% petroleum ether); $[\alpha]_D^{24}$ = -242 (*c*. 1 g/100 mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.01 (1H, ddd, J = 10.0, 7.5, 2.0 Hz), 5.91 (1H, ddt, J = 10.0, 5.0, 1.0 Hz), 5.48 (1H, dddd, J = 11.0, 5.0, 2.0, 1.0 Hz), 5.05 (1H, ddd, J = 6.0, 5.0, 1.0 Hz), 3.78 (3H, s), 1.43 (3H, s), 1.41 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 171.2 (s), 157.8 (d, J = 254.5 Hz), 129.8 (d, J = 10.0 Hz), 121.1 (d, J = 38.5 Hz), 107.5 (s), 99.1 (d, J = 18.0 Hz), 79.6 (d, J = 2.0 Hz), 74.0 (d, J = 12.5 Hz), 53.2 (s), 27.0 (s), 25.0 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -111.7 (dq, J = 11.5, 6.0 Hz); ν_{max} (neat) 2991, 2957, 1737, 1683, 1252, 1040, 802 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{11}H_{13}O_4FNa)^+$ 251.0690, found 251.0707.

((3a*R*,7a*R*)-6-Fluoro-2,2-dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methanol IV-31



Methyl ester **IV-30** (37 mg, 0.162 mmol, 1 equiv.) was dissolved in anhydrous THF (5.0 mL) and cooled to 0°C. $LiBH_4$ (4.0 M in THF, 0.08 mL, 0.324 mmol, 2.0 equiv.) was added slowly, and the solution

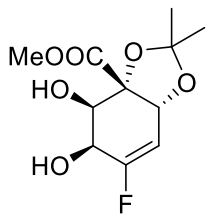
allowed to warm to room temperature over 16 hours. The reaction was quenched with EtOAc (15 mL) and water (15 mL). The organic layer was collected, and the aqueous layer further extracted with EtOAc (2 x 15 mL). Organic layers were combined, dried over $MgSO_4$ and the solvent removed to give **IV-31** as a yellow/orange oil (31 mg, 0.155 mmol, 96%). No purification of the crude product was necessary.

R_f = 0.32 (30% EtOAc, 70% petroleum ether); $[\alpha]_D^{26}$ = -127 (*c*. 1 g/100 mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.94 (1H, ddt, J = 10.7, 6.9, 2.0 Hz), 5.81 (1H, dd, J = 10.3, 5.3 Hz), 5.47 (1H, ddd, J = 10.8, 5.6, 2.0 Hz), 4.65 (1H, t, J = 5.8 Hz), 3.60 (1H, d, J = 11.9 Hz), 3.38 (1H, dd, J = 12.0, 7.2 Hz), 2.08-2.01 (1H, m, O**H**), 1.43 (3H, s), 1.38 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 158.5 (d, J = 255.7 Hz), 133.7 (d, J = 10.1 Hz), 120.7 (d, J = 37.7 Hz), 106.9 (s), 99.2 (d, J = 17.2 Hz), 80.9 (d, J = 1.4 Hz), 71.9 (d, J = 12.6 Hz), 63.7 (s), 27.3 (s), 26.7 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -111.4 (dq, J = 12.1, 6.2 Hz); ν_{max} (film) 3440, 2988, 2936, 2872, 1678, 1373, 1183, 1029, 772 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{10}H_{13}O_3FNa)^+$ 223.0741, found 223.0735.

Methyl (3a*S*,4*R*,5*S*,7a*R*)-6-fluoro-4,5-dihydroxy-2,2-dimethyl-5,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-32

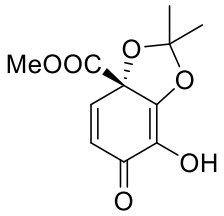
Methyl (*S*)-7-hydroxy-2,2-dimethyl-6-oxobenzo[d][1,3]dioxole-3a(6H)-carboxylate IV-33

To a solution of diene **IV-30** (105 mg, 0.460 mmol, 1.0 equiv.) in acetone (5.0 mL) was added NMO (70 mg, 0.598 mmol, 1.3 equiv.). Water (~0.4 mL) was added until full dissolution of the NMO occurred, and then OsO_4 (2.5 wt% in *t*BuOH, 0.23 mL, 23.0 µmol, 5 mol%) was added. The solution was stirred for 16 hours, during which the solution turned dark brown in colour. The reaction was quenched with addition of aq. $Na_2S_2O_3$ (1.0 M, 10 mL) followed by aq. sat. $NaHCO_3$ (5.0 mL). The product was extracted with EtOAc (3 x 15 mL). Organic layers were combined, washed with brine (30 mL), dried over $MgSO_4$ and the solvent removed to give a dark brown oil, which was a mixture of 2 different products. These were separated by column chromatography (30% EtOAc, 70% petroleum ether → 50% EtOAc, 50% petroleum ether) to give white solid **IV-32** (80 mg, 0.305 mmol, 66%) and yellow oil **IV-33** (6 mg, 25.0 µmol, 5%).



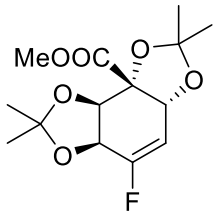
Data for **IV-32**: R_f = 0.27 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{24}$ = -24 (*c*. 0.25 g / 100 mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.52 (1H, dd, J = 14.0, 4.5 Hz), 5.01 (1H, t, J = 5.0 Hz), 4.42-4.36 (1H, m), 4.29-4.24 (1H, m), 3.86 (3H, s), 3.63 (1H, d, J = 9.0 Hz), 3.10-3.02 (1H, m), 1.50 (3H, s), 1.41 (3H, s); ^{13}C

NMR (126 MHz, $CDCl_3$) δ = 172.9 (s), 159.6 (d, J = 269.0 Hz), 111.8 (s), 102.2 (d, J = 17.5 Hz), 83.8 (d, J = 2.0 Hz), 74.0 (d, J = 13.0 Hz), 72.4 (d, J = 8.0 Hz), 65.3 (d, J = 24.5 Hz), 53.4 (s), 27.9 (s), 25.8 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -110.1--110.4 (m); ν_{max} (film) 3405, 3327, 2991, 2950, 1748, 1703, 1257, 1241, 1088, 1053, 857 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{11}H_{15}O_6FNa)^+$ 285.0745, found 285.0728.



Data for **IV-33:** R_f = 0.30 (30% EtOAc, 70% petroleum ether); $[\alpha]_D^{26}$ = -120 (*c*. 0.2 g/100 mL, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ = 6.88 (1H, d, J = 9.7 Hz), 6.34 (1H, d, J = 9.7 Hz), 5.67 (1H, s), 3.77 (3H, s), 1.66 (3H, s), 1.61 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 183.0, 169.0, 145.8, 137.8, 129.9, 128.6, 120.1, 83.4, 54.2, 28.6, 25.7; ν_{max} (film) 3392, 3000, 2956, 1744, 1649, 1598, 1380, 1220, 1140, 1111, 823 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{11}H_{12}O_6Na)^+$ 263.0526, found 263.0537.

Methyl (3a*S*,5a*R*,8a*R*,8b*R*)-4-fluoro-2,2,7,7-tetramethyl-3a,8b-dihydrobenzo[1,2-d:3,4-d']bis([1,3]dioxole)-8a(5aH)-carboxylate IV-35

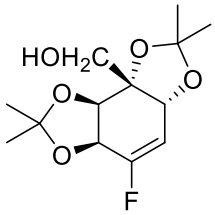


Diol **IV-32** (31 mg, 0.122 mmol, 1.0 equiv.) was dissolved in 2,2-dimethoxypropane (5.0 mL) and *p*TSA added (monohydrate, 3 mg, 15.8 µmol, 13 mol%). The solution was stirred for 48 h. Aqueous saturated $NaHCO_3$ (15 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 x 15 mL). The organic phases were combined, dried over $MgSO_4$ and the solvent removed. The resulting oil was purified by column chromatography (20% EtOAc, 80% petroleum ether) to give **IV-35** as a colourless oil (30 mg, 99.3 µmol, 81%).

R_f = 0.29 (20% EtOAc, 80% petroleum ether); $[\alpha]_D^{24}$ = -34 (*c*. 1 g/100 mL, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ = 5.43 (1H, ddd, J = 6.2, 3.3, 1.5 Hz), 5.31 (1H, dd, J = 15.1, 3.3 Hz), 4.76 (1H, t, J = 5.9 Hz), 4.70 (1H, dd, J = 5.6, 1.5 Hz), 3.85 (3H, s), 1.39 (3H, s), 1.36 (3H, s), 1.35 (3H, s), 1.30 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.9 (s), 156.2 (d, J = 265.1 Hz), 111.55 (s), 111.53 (s), 103.9 (d, J = 14.0 Hz), 82.3 (d, J = 2.1 Hz), 75.8 (d, J = 7.2 Hz), 73.1 (d, J = 11.0 Hz), 70.1 (d, J = 24.0), 53.2 (s), 28.3 (s), 27.84 (s), 27.78 (s), 26.5 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -117.7 (dt, J = 15.1, 6.2 Hz); ν_{max} (film) 2991, 2943, 1747,

1708, 1372, 1223, 1069, 1050, 851 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{14}H_{19}O_6FNa)^+$ 325.1058, found 325.1076.

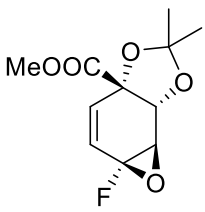
((3a*S*,5a*R*,8a*R*,8b*R*)-4-Fluoro-2,2,7,7-tetramethyl-3a,8b-dihydrobenzo[1,2-d:3,4-d']bis([1,3]dioxole)-8a(5aH)-yl)methanol IV-36



Methyl ester **IV-35** (18 mg, 59.6 µmol, 1.0 equiv.) was dissolved in anhydrous THF (5.0 mL) and the solution was cooled to 0°C. $LiBH_4$ (4.0 M, 0.03 mL, 0.119 mmol, 2.0 equiv.) was added dropwise and the solution allowed to warm to room temperature over 16 hours. EtOAc (15 mL) was added slowly, followed by water (15 mL). The Organic layer was collected and the product further extracted from the aqueous layer with EtOAc (2 x 15 mL). Organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed. The resulting oil was purified by column chromatography (30% EtOAc, 70% petroleum ether) to **IV-36** as a colourless oil (15 mg, 54.7 µmol, 92%).

R_f = 0.29 (30% EtOAc, 70% petroleum ether); $[\alpha]_D^{24}$ = -26 (*c*. 0.5 g/100 mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.33 (1H, dd, J = 15.2, 3.3 Hz), 4.70 (1H, dd, J = 6.6, 5.2 Hz), 4.68-4.64 (2H, m), 3.86 (1H, t, J = 10.6 Hz), 3.79 (1H, d, J = 11.4 Hz), 2.25 (1H, d, J = 9.7, O**H**), 1.45 (3H, s), 1.41 (6H, s), 1.36 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 157.3 (d, J = 266 Hz), 110.7 (s), 111.0 (s), 103.8 (d, J = 14.2), 81.6 (s), 75.6 (d, J = 7.3 Hz), 73.6 (d, J = 10.9 Hz), 70.1 (d, J = 22.8), 64.6 (s), 29.8 (s), 28.8 (s), 27.9 (s), 26.6 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = 117.0 (dt, J = 15.6, 6.3 Hz); ν_{max} (film) 3511, 2990, 2937, 1706, 1371, 1230, 1174, 1085, 1042, 917, 859 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{13}H_{19}O_5FNa)^+$ 297.1109, found 297.1122.

Methyl (3a*S*,5a*R*,6a*R*,6b*R*)-5a-fluoro-2,2-dimethyl-6a,6b-dihydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxole-3a(5aH)-carboxylate IV-38

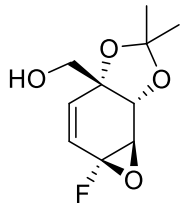


Diene **IV-30** (0.031 g, 0.136 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (3.0 mL) and the solution was cooled to ~0°C. mCPBA (77%, 0.040 g, 0.177 mmol, 1.3 equiv.) was added and the solution was allowed to warm to room temperature over 16 hours. The reaction was quenched with the addition of aqueous $Na_2S_2O_3$ (1.0 M, 10 mL) and the product extracted with CH_2Cl_2 (3 x 10 mL). Organic layers were

combined and washed with a saturated aqueous solution of $NaHCO_3$ (15 mL), before being dried over $MgSO_4$. The solvent was removed to give a yellow/orange liquid, which was purified by column chromatography (10% EtOAc, 90% petroleum ether) to give **IV-38** as a colourless liquid (26 mg, 0.107 mmol, 79%).

R_f = 0.44 (20% EtOAc, 80% petroleum ether); $[\alpha]_D^{24}$ = -64 (*c*. 0.25 g/100 mL, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.29 (1H, dd, J = 10.5, 4.0 Hz), 5.89 (1H, ddd, J = 10.5, 5.5, 1.0 Hz), 5.05 (1H, dt, J = 5.0, 1.5 Hz), 3.90 (1H, t, J = 1.5 Hz), 3.78 (3H, s), 1.46 (3H, s), 1.44 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.0 (s), 131.6 (d, J = 13.0 Hz), 123.46 (d, J = 41.0 Hz), 112.9 (s), 89.9 (d, J = 262.0 Hz), 79.8 (s), 74.2 (d, J = 4.0 Hz), 53.6 (d, J = 17.5 Hz), 53.4 (s), 27.6 (s), 25.7 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -148.0 (q, J = 5.0 Hz); ν_{max} (film) 2992, 2957, 1745, 1378, 1263, 1192, 1057, 969 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{11}H_{13}O_5FNa)^+$ 267.0639, found 267.0649.

((3a*R*,5a*R*,6a*R*,6b*R*)-5a-Fluoro-2,2-dimethyl-6a,6b-dihydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxol-3a(5aH)-yl)methanol IV-40



Methyl ester **IV-38** (64 mg, 0.259 mmol, 1.0 equiv.) was dissolved in anhydrous THF (3.0 mL) and the solution was cooled to ~0°C. $LiBH_4$ (4.0 M in THF, 0.13 mL, 0.518 mmol, 2.0 equiv.) was added slowly over 5 minutes. The solution was allowed to warm to room temperature over 24 hours, after which EtOAc (10 mL) was added slowly, followed by H_2O (10 mL). The organic layer was collected, and the aqueous layer further extracted with EtOAc (2 x 10 mL). Organic layers were combined and dried over $MgSO_4$. The solvent was removed to give **IV-40** as a pale yellow oil (41 mg, 0.190 mmol, 73%).

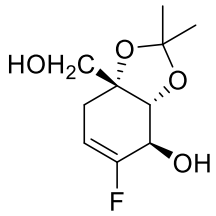
R_f = 0.34 (25% EtOAc, 75% petroleum ether); $[\alpha]_D^{24}$ = -28 (*c.* 1 g/100 mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.24 (1H, dd, J = 10.5, 4.0 Hz), 5.74 (1H, ddd, J = 10.5, 5.5, 1.5 Hz), 4.61 (1H, ddd, J = 5.0, 2.0, 1.5 Hz), 3.92 (1H, t, J = 1.5 Hz), 3.59 (1H, d, J = 12.0 Hz), 3.34 (1H, br. d, J = 11.5 Hz), 1.89 (1H, m, O**H**), 1.43 (3H, s), 1.41 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 134.2 (d, J = 13.0 Hz), 123.3 (d, J = 41.0 Hz), 111.1 (s), 90.3 (d, J = 262.0 Hz), 81.5 (s), 71.2 (d, J = 4.0 Hz), 64.9 (s), 54.5 (d, J = 17.5 Hz), 28.1 (s), 27.0 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -146.7 (q, J = 5.0 Hz); ν_{max} (film) 3461, 2993, 2930, 2856, 1459, 1196, 1078, 1051 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{10}H_{13}O_4FNa)^+$ 239.0690, found 239.0721.

(3a*R*,4*R*,7a*R*)-5-Fluoro-7a-(hydroxymethyl)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol IV-41

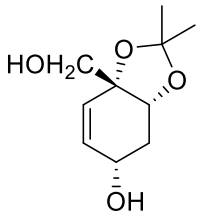
(3a*R*,5*S*,7a*R*)-7a-(Hydroxymethyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-ol IV-42

(3a*R*,5*R*,7a*R*)-7a-(Hydroxymethyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-ol IV-43

To solid $LiAlH_4$ (59 mg, 1.55 mmol, 3.2 equiv.) was added anhydrous Et_2O (5.0 mL). The suspension was cooled to 0°C. A solution of epoxide **IV-38** (0.120 g, 0.486 mmol, 1.0 equiv.) in anhydrous Et_2O (2.0 mL) was then added, and the suspension allowed to warm to room temperature over 16 hours. After this time, the suspension was again cooled to 0°C and EtOAc (5.0 mL) added slowly to quench the reaction, followed by water (5.0 mL). The biphasic solution was filtered. The organic layer was collected, and the product further extracted from the aqueous phase with EtOAc (3 x 5.0 mL). Organic layers were combined, dried over $MgSO_4$ and the solvent removed. The crude product was purified by column chromatography (50% EtOAc, 50% petroleum ether → 100% EtOAc) to give 3 products: **IV-41** (23 mg, 0.105 mmol, 22%), **IV-42** (15 mg, 75 µmol, 15%), **IV-43** (21 mg, 0.105 mmol, 22%).

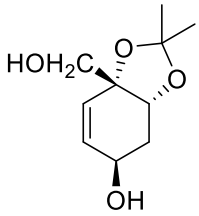


Data for **IV-41**. R_f = 0.29 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = +35 (*c*. 0.67 g/100 mL, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.31 (1H, dt, J = 14.5, 4.4 Hz), 4.25 (1H, dd, J = 6.1, 2.0 Hz), 3.69 (1H, d, J = 11.0 Hz), 3.65 (1H, d, J = 11.0 Hz), 2.46 (1H, dddd, J = 18.0, 5.1, 4.4, 0.6 Hz), 2.39 (1H, dddd, J = 18.1, 5.5, 4.4, 1.0 Hz), 1.43 (3H, s), 1.39 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 157.7 (d, J = 256.0 Hz), 108.9 (s), 102.6 (d, J = 16.7 Hz), 81.9 (d, J = 8.6 Hz), 79.3 (d, J = 1.5 Hz), 67.3 (s), 65.5 (d, J = 28.6 Hz), 31.5 (d, J = 6.8 Hz), 28.0 (s), 26.9 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -117.3 (tt, J = 13.9, 5.7 Hz); ν_{max} (film) 3379, 2991, 2931, 1441, 1373, 1218, 1173, 1148, 908 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{10}H_{15}O_4FNa)^+$ 241.0847, found 241.0852.



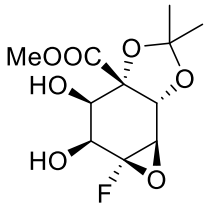
Data for **IV-42**. R_f = 0.14 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = +23 (CH_2Cl_2, *c.* 0.667 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.92 (1H, dt, J = 10.4, 1.8 Hz), 5.43 (1H, dt, J = 10.4, 2.0 Hz), 4.49 (1H, ddt, J = 10.0, 5.5, 2.1 Hz), 4.40 (1H, dt, J = 3.9, 2.0 Hz), 3.61 (1H, d, J = 12.0 Hz), 3.44 (1H, d, J = 12.0 Hz), 2.54 (1H, dddd, J = 14.0, 5.5, 3.8, 1.6 Hz), 1.60 (1H, ddd, J = 14.0, 10.0, 2.2 Hz), 1.38 (3H, s), 1.35 (3H, s); ^{13}C

NMR (126 MHz, $CDCl_3$) δ = 134.9, 127.6, 108.2, 79.4, 73.8, 63.8, 63.7, 34.1, 27.7, 27.1; ν_{max} (film) 3355, 2987, 2931, 2871, 1371, 1220, 997 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{10}H_{16}O_4Na)^+$ 223.0941, found 223.0950.



Data for **IV-43**. R_f = 0.17 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = -60 (*c.* 0.5 g/100 mL, $CHCl_3$); ^1H NMR (500 MHz, CDCl3) δ = 6.09 (1H, ddd, J = 10.2, 5.1, 1.5 Hz), 5.49 (1H, dd, J = 10.2, 1.7 Hz), 4.53-4.46 (1H, m), 4.10-4.03 (1H, m), 3.62 (1H, d, J = 12.1 Hz), 3.39 (1H, dd, J = 12.4, 6.6 Hz), 3.08 (1H, d, J = 11.2 Hz), 2.45 (1H, ddt, J = 15.6, 3.5, 1.7 Hz), 2.00 (1H, d, J = 7.8 Hz), 1.95 (1H, ddd, J = 15.6, 4.7, 2.2 Hz), 1.46 (3H, s), 1.39 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) 131.6, 128.0, 108.9, 79.8, 73.5, 62.9, 62.4, 30.8, 28.0, 26.9;); ν_{max} (film) 3405, 2988, 2930, 1380, 1226, 1167, 818 cm^{-1}; HRMS (ESI+) *m/z* calculated for $(C_{10}H_{16}O_4Na)^+$ 223.0941, found 223.0948.

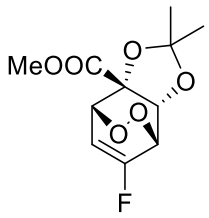
Methyl (3a*S*,4*R*,5*S*,5a*R*,6a*R*,6b*R*)-5a-fluoro-4,5-dihydroxy-2,2-dimethyltetrahydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxole-3a(4H)-carboxylate IV-46



Diol **IV-32** (37 mg, 0.141 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5.0 mL) and *m*CPBA (100%, 37 mg, 0.212 mmol, 1.5 equiv.) added. After 24 h, a further quantity of *m*CPBA (100%, 37 mg, 0.212 mmol, 1.5 equiv.) was added. The solution was stirred for 5 days. Aqueous sodium thiosulfate (1.0 M, 10 mL) was added, and the product extracted with CH_2Cl_2 (3 x 15 mL). Organic layers were combined, dried over $MgSO_4$ and the solvent removed. The resulting solid was purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **IV-46** as a white solid (22 mg, 79.1 µmol, 56%).

R_f = 0.30 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{24}$ = +9.3 (*c*. 0.75 g/100 mL, CH_2Cl_2); melting point = 133-135°C; ^1H NMR (500 MHz, $CDCl_3$) δ = 5.15 (1H, dd, J = 5.8, 0.9 Hz), 4.70 (1H, d, J = 4.5 Hz), 4.35-4.28 (1H, m), 3.84 (3H, s), 3.72 (1H, s), 2.94 (s, O**H**), 2.54 (1H, d, J = 11.3 Hz, O**H**), 1.45 (3H, s), 1.33 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.8 (s), 112.8 (s), 93.8 (d, J = 280.3 Hz), 85.4 (s), 72.5 (d, J = 3.1 Hz), 70.4 (d, J = 6.7 Hz), 64.3 (d, J = 23.5 Hz), 59.6 (d, J = 17.6 Hz), 53.4 (s), 28.1 (s), 26.8 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ -146.5 (t, J = 5.3 Hz) ; ν_{max} (film) 3504, 3490, 2994, 2959, 1741, 1727, 1235, 1208, 1094, 1033, 858 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{11}H_{15}O_7FNa)^+$ 301.0694, found 301.0709.

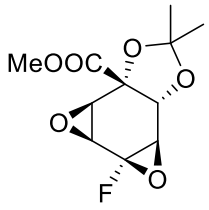
Methyl (3a*R*,4*R*,7*R*,7a*R*)-6-fluoro-2,2-dimethyl-7,7a-dihydro-4,7-epidioxybenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-47



A solution of diene **IV-30** (0.114 g, 0.500 mmol) and TPP (3 mg) in CH_2Cl_2 (10 mL) in Schlenk tube was cooled to ~2°C. Five white 12 V LED lights, attached to the outside of the vessel using an elastic band, were used to irradiate the solution. O_2 gas from a cylinder was bubbled through the solution for 12 hours. During this period, care was taken to ensure the solvent volume remained at around 10 mL, with additional solvent being added as necessary to replace that which had evaporated. After 12 hours, the solvent was removed under vacuum. Crude ^{1}H NMR indicated ~70% conversion of the starting material, which was not improved upon through longer reaction times or increasing quantity of photosensitiser. As such, the solvent was removed and the crude product purified by column chromatography (10% EtOAc, 90% petroleum ether) to give **IV-47** as a colourless oil (77 mg, 0.296 mmol, 59%).

R_f = 0.31 (10% EtOAc, 90% petroleum ether); $[\alpha]_D^{25}$ = -41 (CH_2Cl_2, *c.* 1 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.76 (1H, ddd, J = 7.1, 4.1, 2.7 Hz), 5.33 (1H, ddt, J = 7.1, 5.4, 0.8 Hz), 5.18 (1H, dd, J = 5.2, 3.7 Hz), 4.94 (1H, dddd, J = 9.7, 5.2, 2.8, 1.0 Hz), 3.88 (3H, s), 1.38 (3H, s), 1.34 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.5 (s), 159.6 (d, J = 294.8 Hz), 113.0 (s), 101.4 (d, J = 4.4 Hz), 80.9 (s), 75.2 (d, J = 9.1 Hz), 73.5 (d, J = 3.0 Hz), 53.5 (s), 26.4 (s), 26.4 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -102.7 to -102.9 (m); ν_{max} (film) 2960, 1742, 1686, 1376, 1261, 1066, 1063, 811 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{11}H_{13}O_6FNa)^+$ 283.0588, found 283.0614.

Methyl (1a*S*,1b*S*,2a*R*,2b*S*,5a*R*,5b*R*)-1a-fluoro-4,4-dimethyltetrahydrobis(oxireno)[2',3':3,4;2'',3'':5,6]benzo[1,2-d][1,3]dioxole-2b(1aH)-carboxylate IV-48

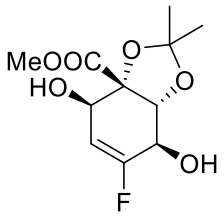


To a solution of endoperoxide **IV-47** (32 mg, 124 μmol) in CH_2Cl_2 (2.0 mL) was added Co(TPP) (1 mg). The solution was stirred at RT for 16 h. The solvent was removed under vacuum and the product

purified by column chromatography (10% EtOAc, 90% petroleum ether) to give fluoro-(bis)epoxide **IV-48** as a colourless oil (22 mg, 84 µmol, 68%).

R_f = 0.17 (10% EtOAc, 90% petroleum ether); $[\alpha]_D^{25}$ = -51 (CH_2Cl_2, *c.* = 0.667 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.89 (1H, dd, J = 5.8, 1.1 Hz), 3.86 (3H, s), 3.85 (1H, d, J = 3.8 Hz), 3.67 (1H, dd, J = 2.9, 1.1 Hz), 3.52 (1H, d, J = 3.7 Hz), 1.48 (3H, s), 1.40 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ = 169.6 (s), 112.3 (s), 91.1 (d, J = 269.4 Hz), 79.9 (s), 73.6 (d, J = 3.5 Hz), 55.2 (d, J = 19.5 Hz), 53.5 (s), 52.7 (d, J = 5.7 Hz), 49.7 (d, J = 54.1 Hz), 27.7 (s), 25.7 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -140.8 (dt, J = 6.4, 3.5 Hz); ν_{max} (film) 2994, 2942, 1746, 1438, 1376, 1261, 1186, 980 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{11}H_{13}O_6FNa)^+$ 283.0588, found 283.0616.

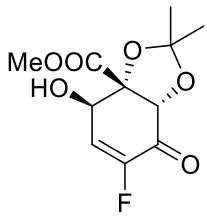
Methyl (3a*S*,4*R*,7*R*,7a*R*)-6-fluoro-4,7-dihydroxy-2,2-dimethyl-7,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-49



To a solution of endoperoxide **IV-47** (39 mg, 0.150 mmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL) and MeOH (1.5 mL) was added thiourea (13 mg, 0.168 mmol, 1.1 equiv.). The solution was stirred for 16 h and filtered. The solvent was then removed, and the crude product purified by column chromatography (50% EtOAc, 50% petroleum ether) to give **IV-49** as a colourless oil (32 mg, 0.122 mmol, 81%).

R_f = 0.43 (50% EtOAc, 50% petroleum ether); $[\alpha]_D^{25}$ = -23 (CH_2Cl_2, *c.* 1 g/100 mL); ^{1}H NMR (500 MHz, CD_3OD) δ = 5.64 (1H, ddd, J = 12.2, 6.1, 1.0 Hz), 5.01 (1H, dd, J = 5.6, 2.3 Hz), 4.44 (1H, dd, J = 6.1, 4.3 Hz), 4.18 (1H, dd, J = 10.5, 2.4, 1.0 Hz), 3.80 (3H, s), 1.34 (3H, s), 1.24 (3H, s); ^{13}C NMR (126 MHz,CD_3OD) δ = 173.8 (s), 164.6 (d, J = 271.7 Hz), 110.8 (s), 106.8 (d, J = 13.6 Hz), 86.7 (d, J = 1.4 Hz), 82.6 (d, J = 8.1 Hz), 70.0 (d, J = 11.5 Hz), 68.4 (d, J = 27.6 Hz), 53.1 (s), 27.1 (s), 25.5 (s); ^{19}F NMR (500 MHz,CD_3OD) δ = -109.1 (tt, J = 10.2, 5.0 Hz); ν_{max} (film) 3414, 2991, 2958, 1736, 1691, 1377, 1261, 1162, 1046, 728 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{11}H_{15}O_6FNa)^+$ 285.0745, found 285.0782.

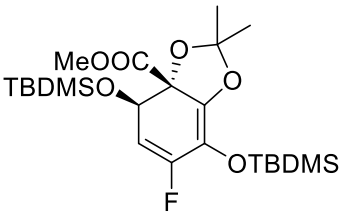
Methyl (3a*S*,4*R*,7a*S*)-6-fluoro-4-hydroxy-2,2-dimethyl-7-oxo-7,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-50



To a solution of endoperoxide **IV-47** (77 mg, 0.296 mmol) in CH_2Cl_2 (5.0 mL) was added DIPEA (10 µL). The solution was stirred for 20 h and the solvent removed under vacuum to give a crude product, which was purified by column chromatography (30% EtOAc, 70% petroleum ether) to give **IV-50** as a colourless oil (8 mg, 30.8 µmol, 13%).

R_f = 0.13 (30% EtOAc, 70% petroleum ether); $[\alpha]_D^{26}$ = -60 (CH_2Cl_2, *c.* 0.333 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.49 (1H, dd, J = 11.9, 4.7 Hz), 4.99 (1H, d, J = 3.6 Hz), 4.91 (1H, q, J = 5.5 Hz), 3.85 (3H, s), 2.84 (1H, d, J = 7.1 Hz, O**H**), 1.41 (3H, s), 1.41 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 185.7 (d, J = 20.3 Hz), 170.0 (s), 152.6 (d, J = 271.1 Hz), 123.0 (d, J = 13.8 Hz), 113.0 (s), 86.7 (d, J = 1.5 Hz), 77.2 (apparent s), 67.5 (d, J = 9.1 Hz), 53.4 (s), 28.0 (s), 26.4 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -127.7 (ddd, J = 12.2, 5.5, 4.0 Hz); ν_{max} (film) 3451, 2994, 2957, 2854, 1741, 1708, 1377, 1259, 1225, 1015, 729 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{11}H_{13}O_6FNa)^+$ 283.0588, found 283.0585.

Methyl (3a*R*,4*R*,7a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-fluoro-2,2-dimethyl-7-oxo-7,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-54



To a solution of endoperoxide **IV-47** (34 mg, 0.131 mmol, 1.0 equiv.) and DMAP (4 mg) in anhydrous CH_2Cl_2 (5.0 mL) was slowly added NEt_3 (0.05 mL, 0.361 mmol, 3.6 equiv.) and TBDMSOTf (0.04 mL, 1.74 mmol, 1.3 equiv.) at 0°C. The solution was allowed to warm to room temperature over 16 h. The reaction was quenched with water (10 mL) and the product extracted with CH_2Cl_2 (3 x 10 mL). Organic layers were combined, dried over $MgSO_4$, and the solvent removed under vacuum to give an orange oil. This oil was purified by column chromatography (5% EtOAc, 95% petroleum ether) to give **IV-54** as a colourless oil (14 mg, 29.8 µmol, 23%).

R_f = 0.35 (5% EtOAc, 95% petroleum ether); $[\alpha]_D^{25}$ = +112 (CH_2Cl_2, *c.* 0.5 g/100 mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.94 (1H, dd, J = 5.8, 2.0 Hz), 4.83 (1H, dd, J = 11.4, 2.0 Hz), 3.74 (3H, s), 1.53 (3H, s), 1.48 (3H, s), 0.94 (9H, s), 0.86 (9H, s), 0.16 (3H, s), 0.16 (3H, s), 0.09 (3H, s), 0.07 (3H, s); ^{13}C NMR (126 MHz,

$CDCl_3$) δ = 169.3 (s), 153.9 (d, J = 259.8 Hz), 135.8 (d, J = 7.7 Hz), 119.9 (d, J = 30.7 Hz), 117.5 (s), 102.2 (d, J = 16.3 Hz), 90.0 (s), 75.3 (d, J = 8.6 Hz), 52.2 (s), 27.9 (s), 26.4 (s), 18.4 (s), 18.2 (s), -4.6 (d, J = 0.8 Hz), -4.7 (s), -4.8 (d, J = 1.2 Hz), -5.0 (s); ^{19}F NMR (500 MHz, $CDCl_3$) δ = -126.9 (dd, J = 11.4, 5.8 Hz); ν_{max} (film) 2954, 2930, 2858, 1760, 1737, 1698, 1655, 1250, 1117, 943 cm^{-1}; HRMS (ESI+) *m/z* calculated $(C_{23}H_{41}O_6FSi_2H)^+$ 489.2498, found 489.2516.

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Appendix

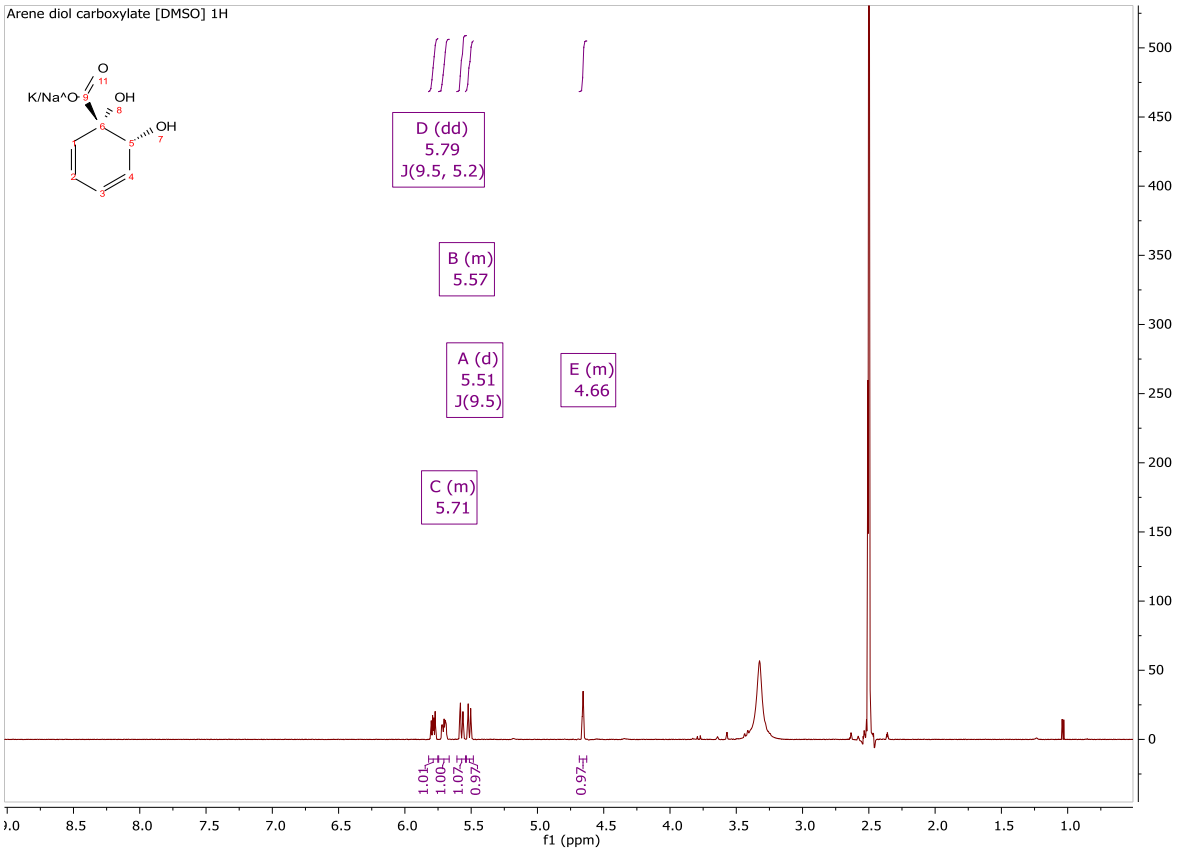
General conditions

All anhydrous reactions were carried out under an atmosphere of N_2 or argon, through the use of a Schlenk line, unless otherwise stated. Anhydrous solvents were either purchased from Fisher Scientific or Sigma-Aldrich, or purified through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Thin layer chromatography (TLC) was carried out on aluminium plates coated with silica gel (Alugram®SIL G/UV 254 nm), and visualisation was achieved with UV light or KMnO4, ceric ammonium molybdate and iodine dips, followed by gentle heating. Solvents were removed using Büchi rotary evaporators and under vacuum on a Schlenk line. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35-70 micron) purchased from Sigma-Aldrich.

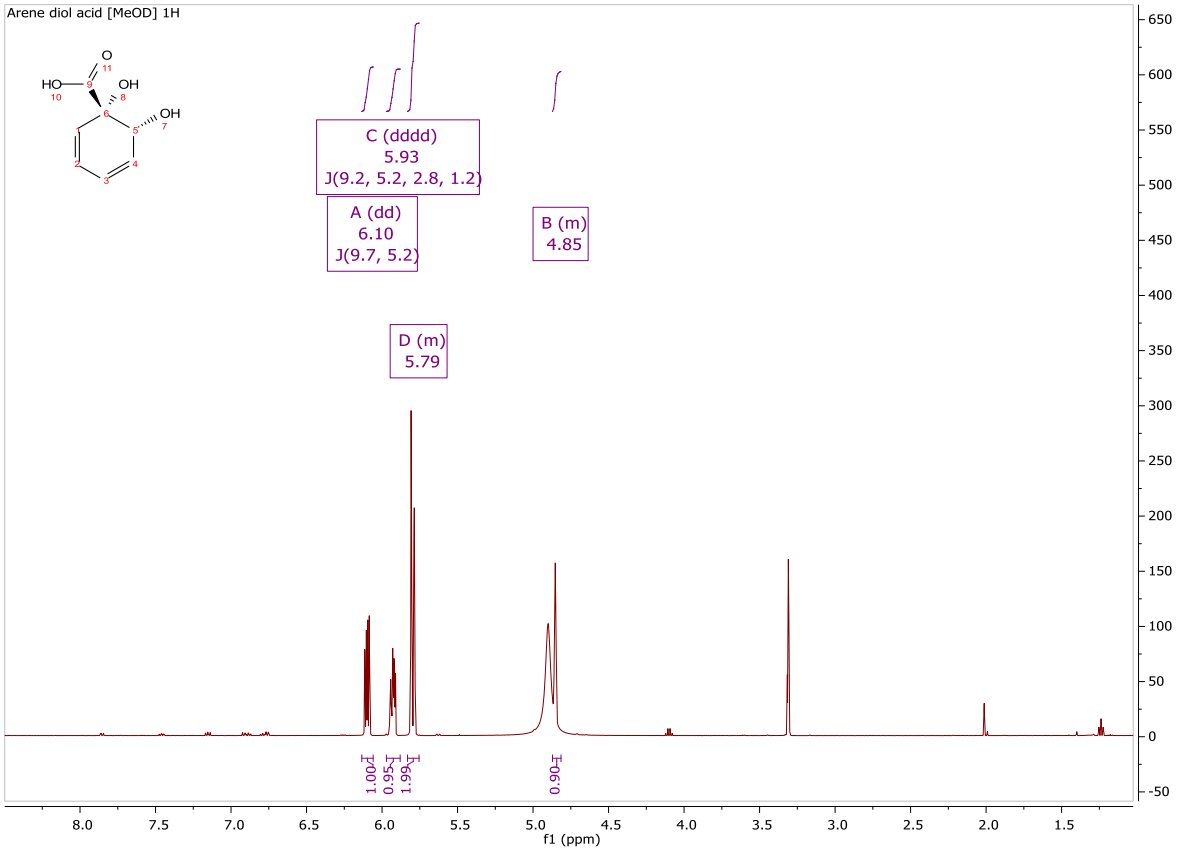
NMR spectra were run in $CDCl_3$ unless otherwise stated, on Bruker Avance 250, Bruker Avance 300, Bruker Avance 400, Bruker Avance 500 II+ or Agilent A500a instruments. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument. Capillary melting points were recorded on a Büchi 535 melting point apparatus and are uncorrected. High resolution mass spectrometry (HRMS) was carried out using a micrOTOF ESI-TOF spectrometer coupled to an Agilent 1200 LC system for autosampling. X-ray crystallography was carried out on a Nonius Kappa CCD diffractometer with Mo-Kα radiation (λ = 0.71073 Å).

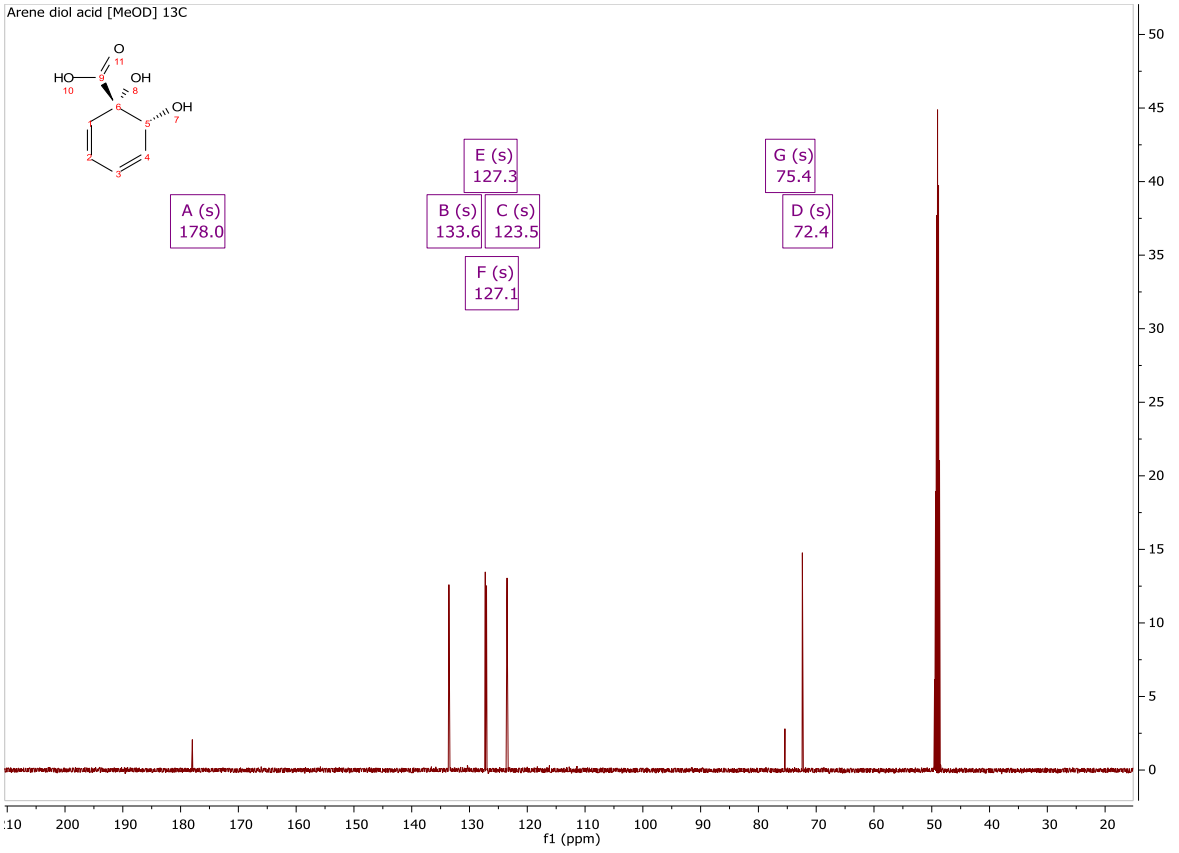
Synthesis of enantiopure heterocycles from an arene *ipso,*ortho-diol: data

Potassium/sodium (1*S*,6*R*)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate II-01

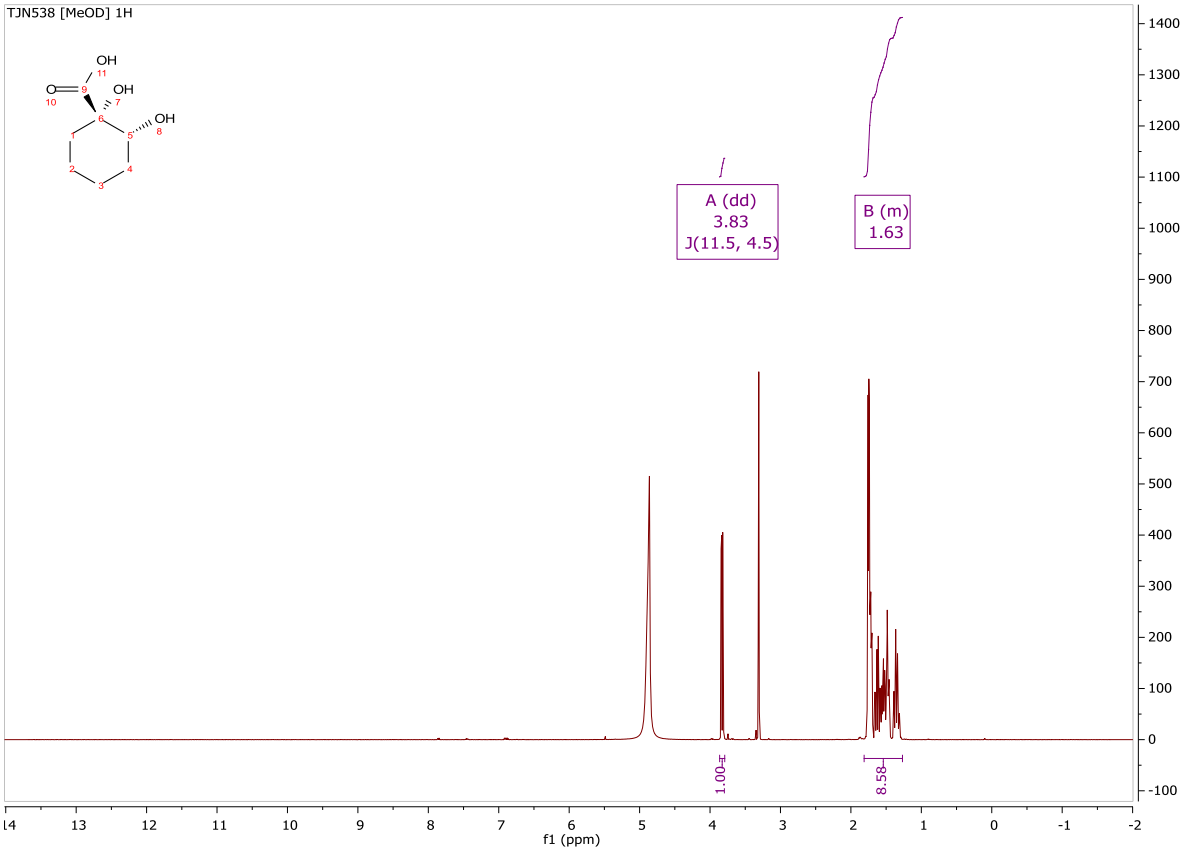


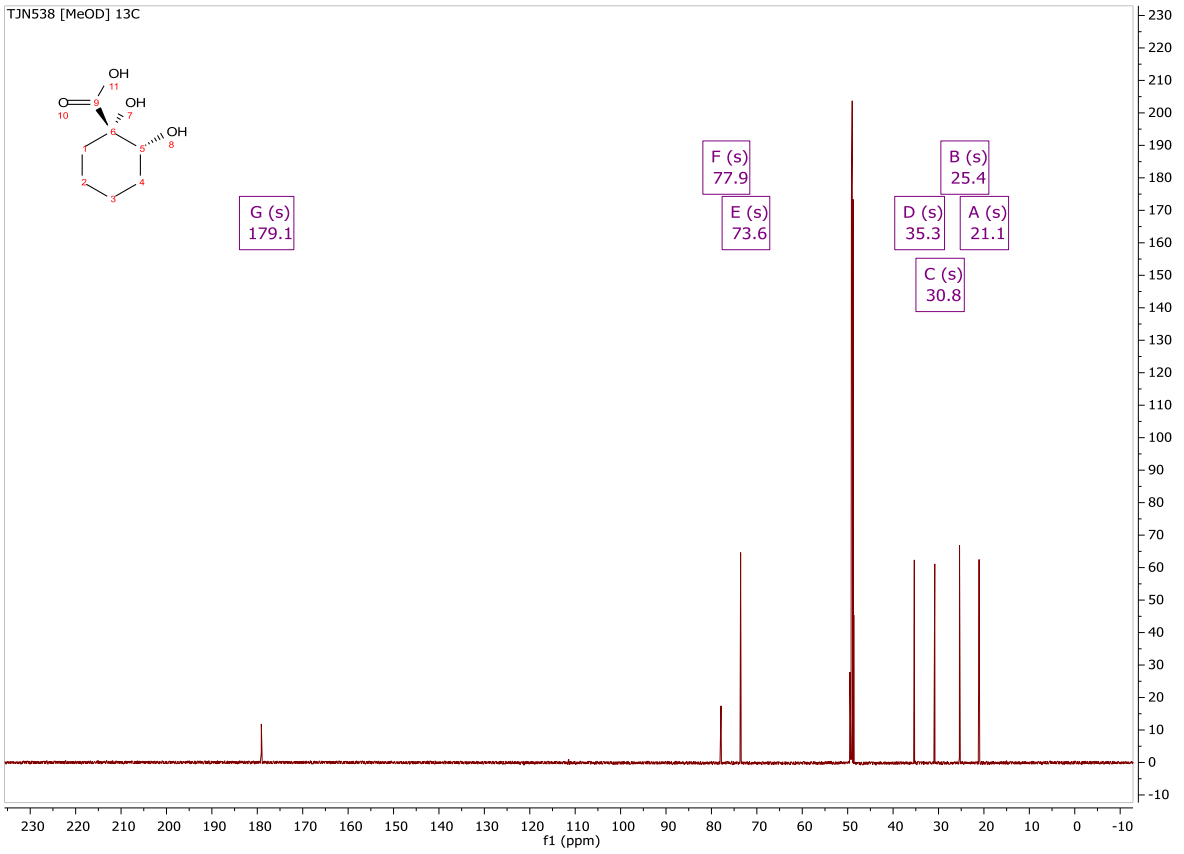
(1*S*,6*R*)-1,6-Dihydroxycyclohexa-2,4-diene-1-carboxylic acid II-06



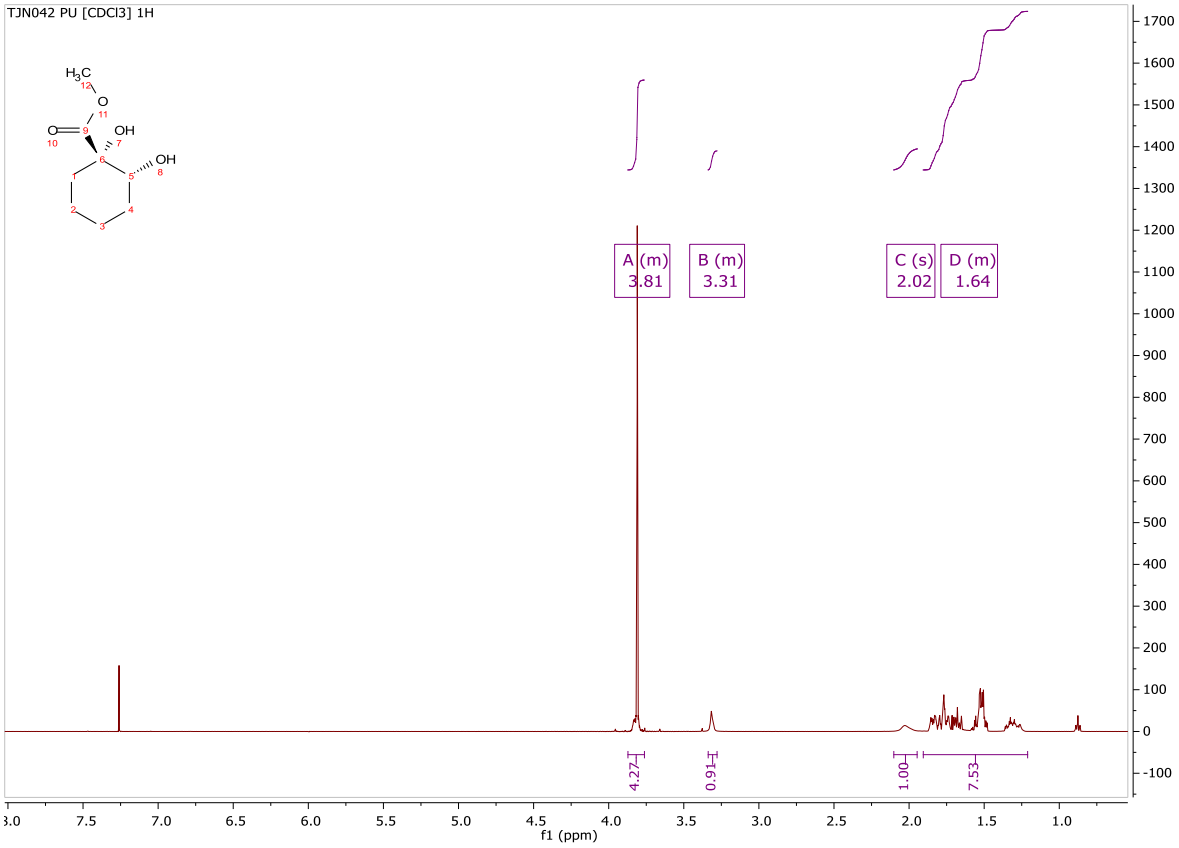


(1*S*,2*R*)-1,2-Dihydroxycyclohexane-1-carboxylic acid II-22





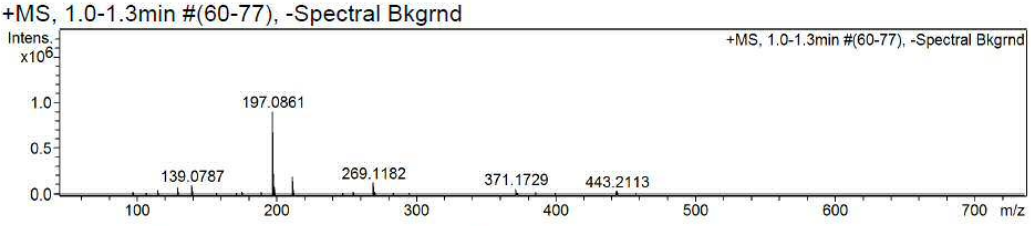
Methyl (1*S*,2*R*)-1,2-dihydroxycyclohexane-1-carboxylate II-23



Confirmation of Expected Formula

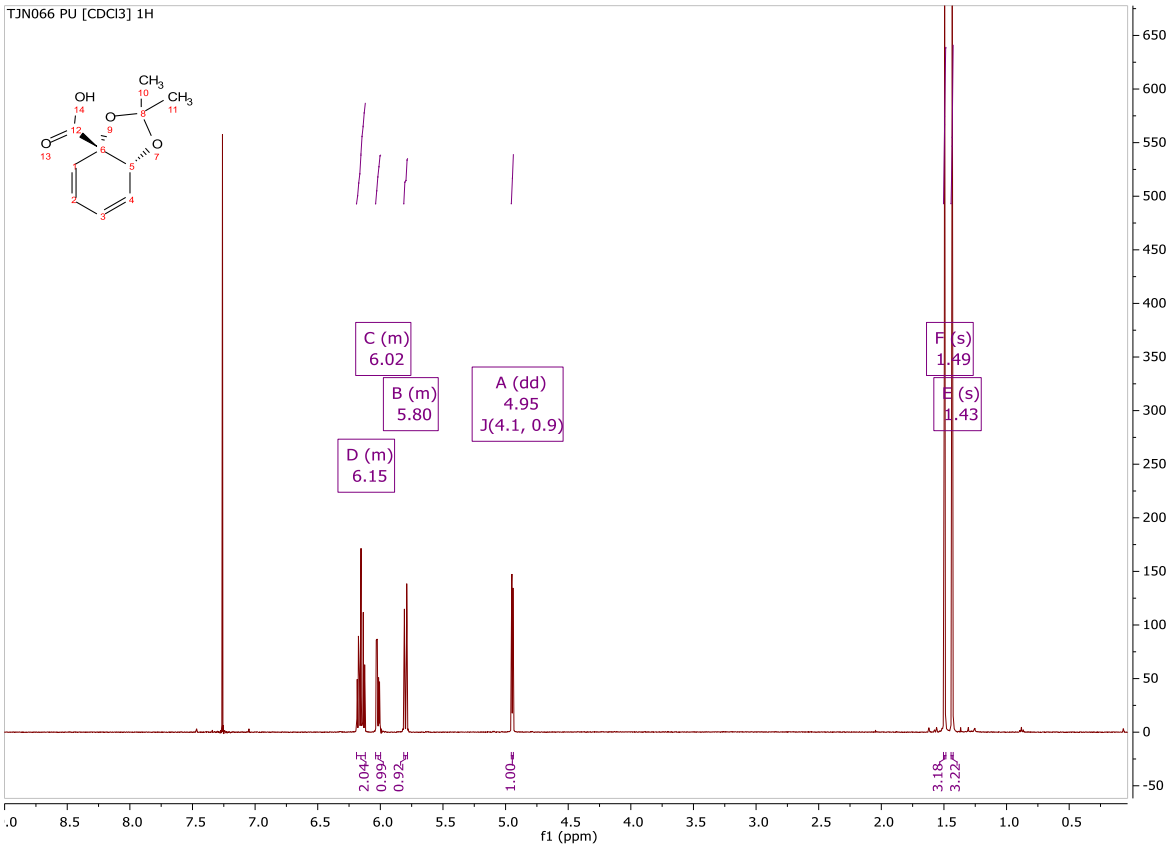
Sample-ID	tn_sel_92	Submitter	Toby Nash
Analysis Name	tn_sel_92_344680_35_01_49194.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	18/08/2015 10:13:46
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	97.0655	29221	3.3	576	6256.4
2	115.0777	45600	5.1	977	6126.4
3	129.0936	74679	8.3	2029	8129.5
4	139.0787	91844	10.2	2600	8807.7
5	197.0861	898260	100.0	21377	13731.5
6	198.0811	71300	7.9	2526	1067.1
7	211.0958	192572	21.4	7496	2604.1
8	269.1182	124742	13.9	5953	3311.9
9	371.1729	57794	6.4	3969	1496.1
10	443.2113	32445	3.6	2922	649.5

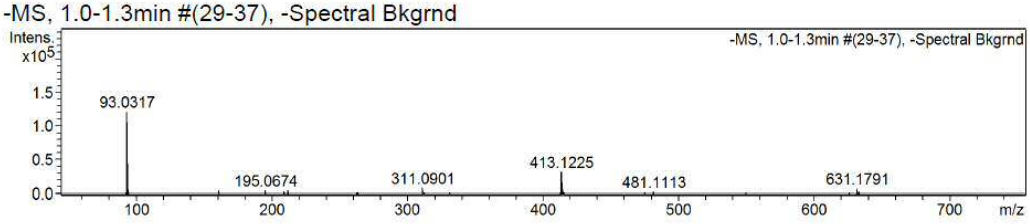
(3a*S*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylic acid II-07



Confirmation of Expected Formula

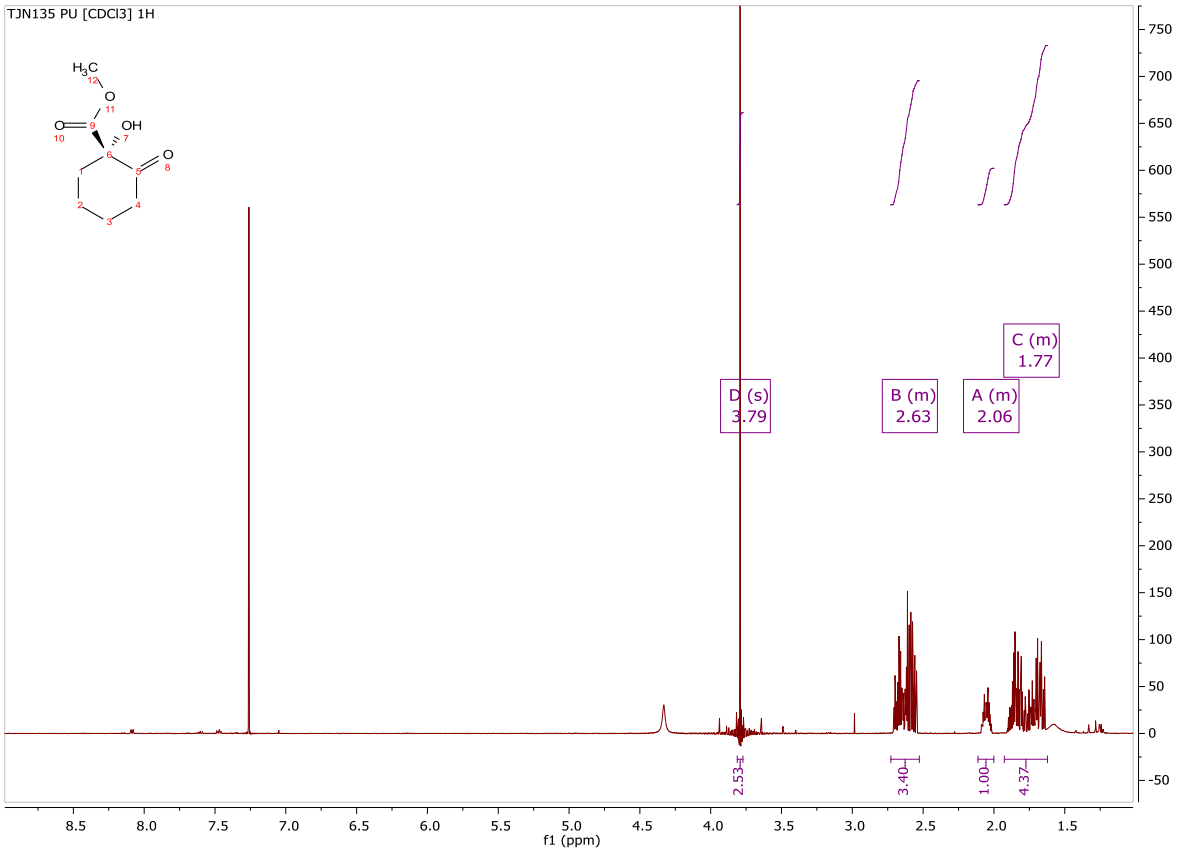
Sample-ID	tn_sel_066	Submitter	Toby Nash
Analysis Name	tn_sel_066_343936_74_01_48351.d	Supervisor	Simon Lewis
Method used	Confirm Formula Negative 50to500 loop inj.m	Acquisition Date	02/06/2015 12:45:57
Ionisation Mode	negative electrospray (ESI)		

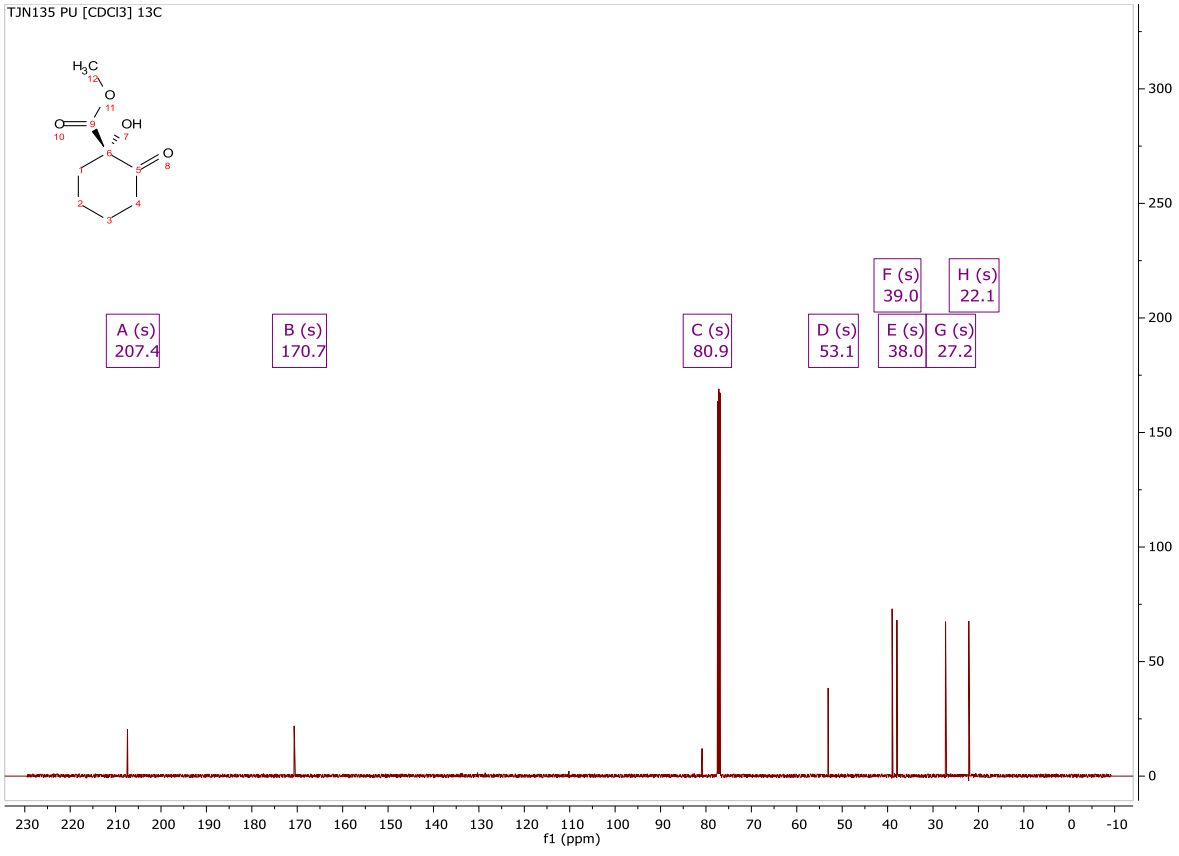
-MS, 1.0-1.3min #(29-37), -Spectral Bkgrnd

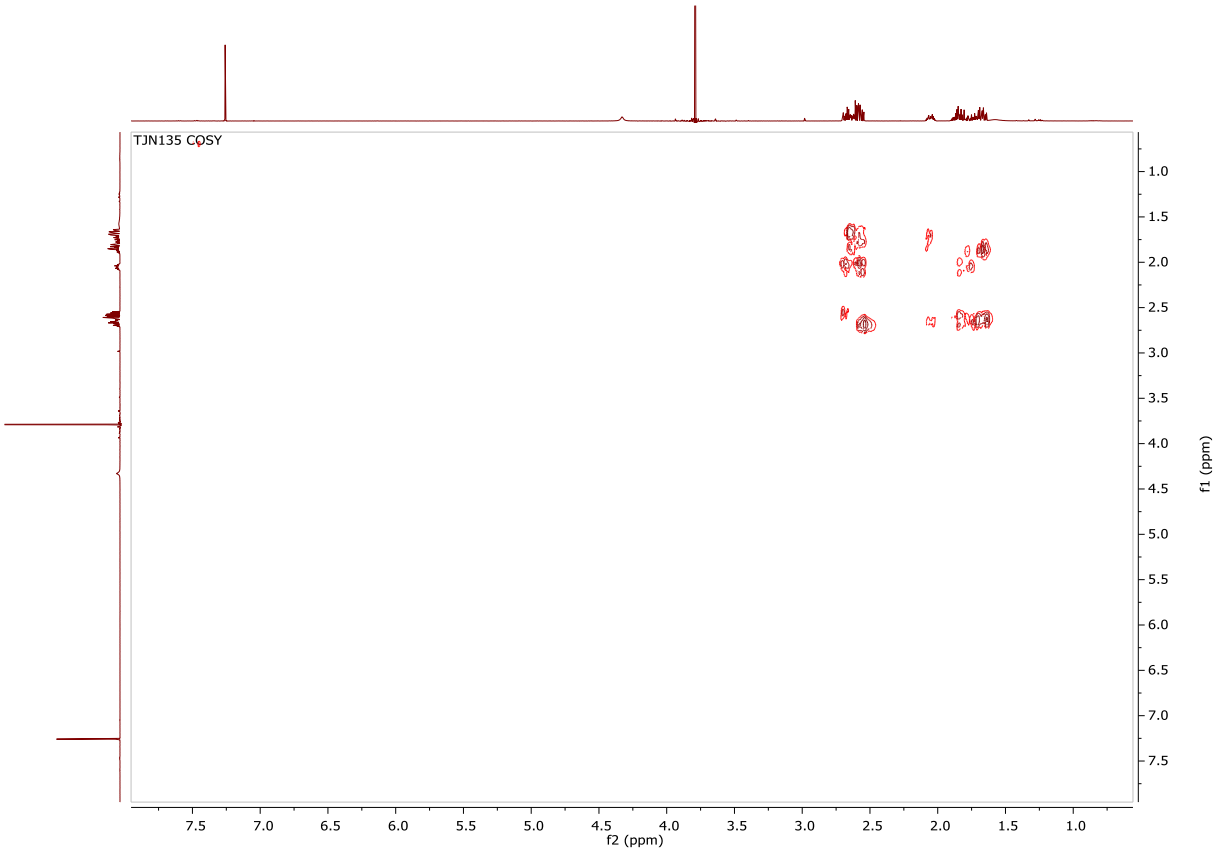


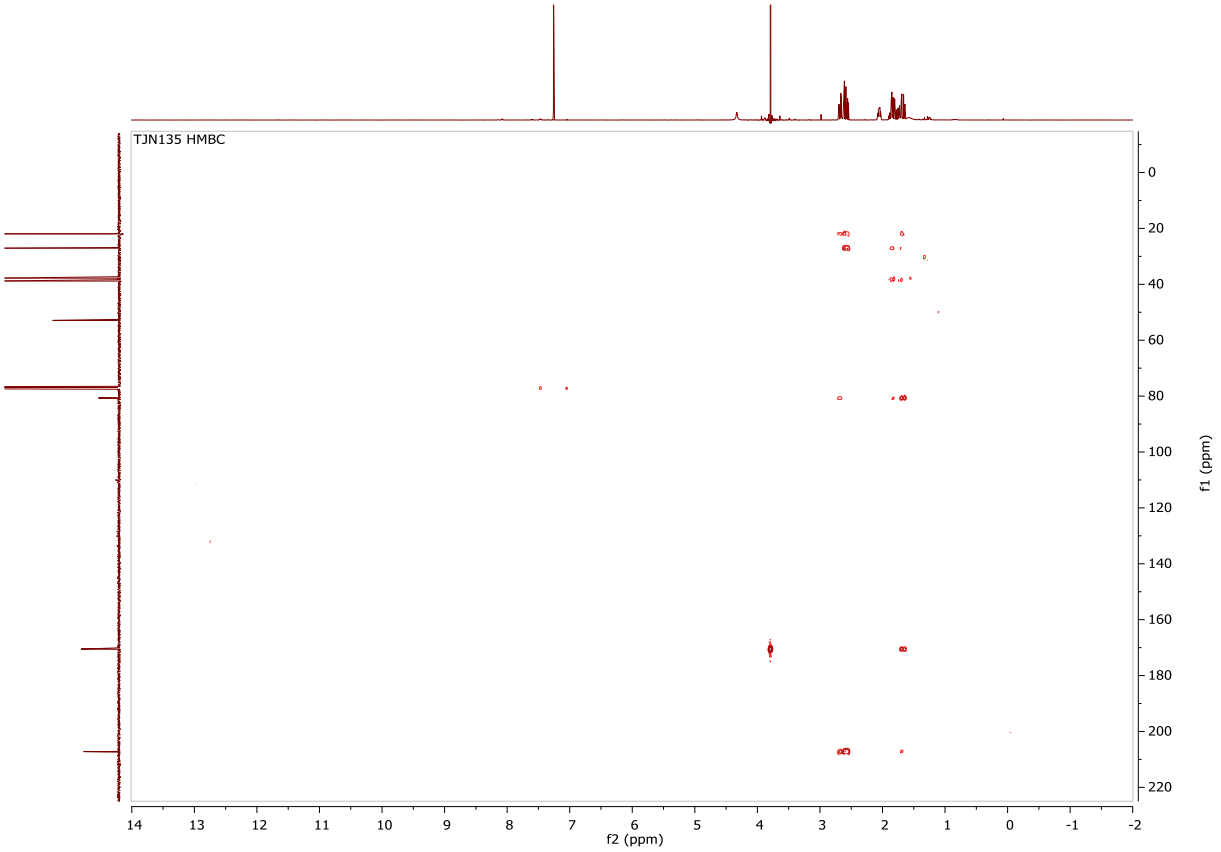
#	m/z	I	I %	Area	S/N
1	93.0317	121185	100.0	2778	17623.1
2	94.0353	8474	7.0	189	1246.7
3	161.0240	4793	4.0	130	1528.0
4	195.0674	5368	4.4	184	1382.3
5	209.0590	3122	2.6	120	734.2
6	212.0776	5011	4.1	74	1182.5
7	311.0901	8832	7.3	482	1862.9
8	413.1225	32163	26.5	2184	6790.5
9	414.1267	6884	5.7	486	1473.5
10	631.1791	7984	6.6	801	650.8

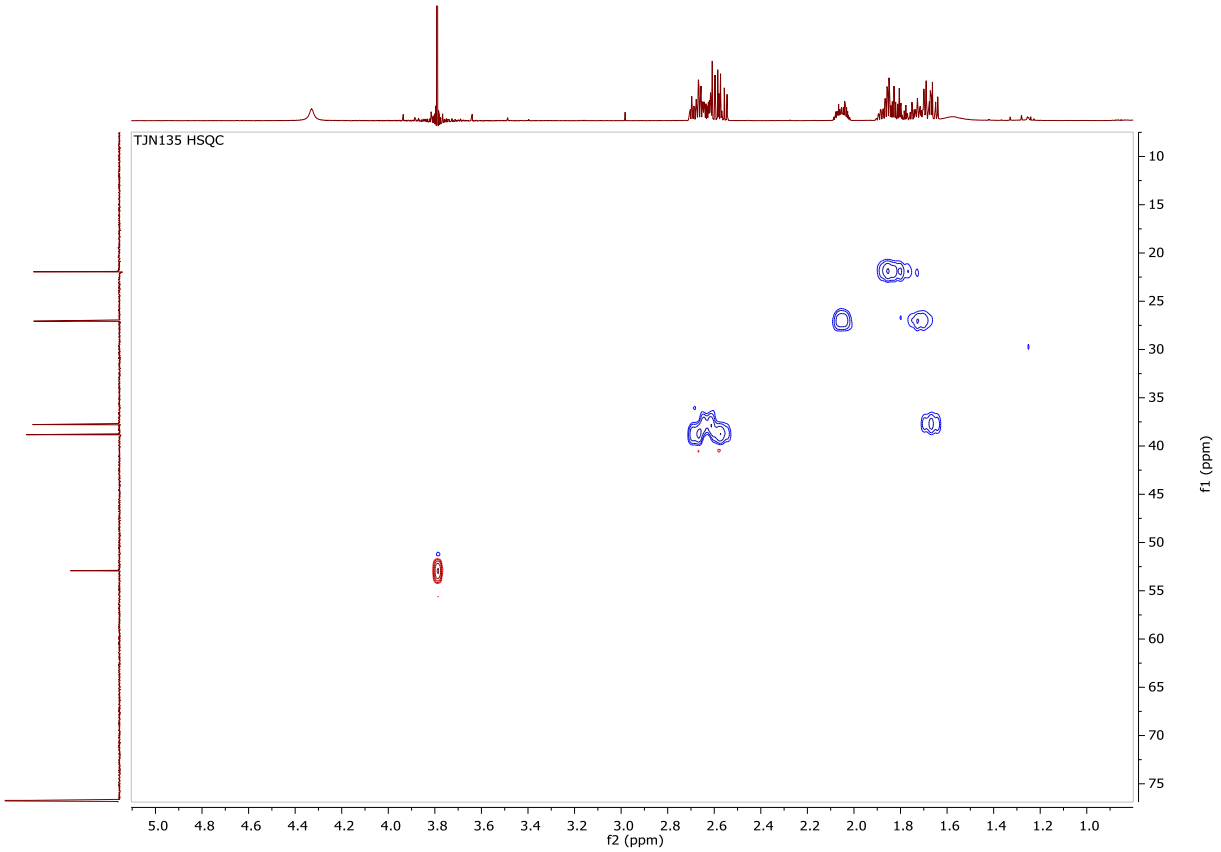
Methyl (*S*)-1-hydroxy-2-oxocyclohexane-1-carboxylate II-25






TJN135 COSY
f2 (ppm)
f1 (ppm)

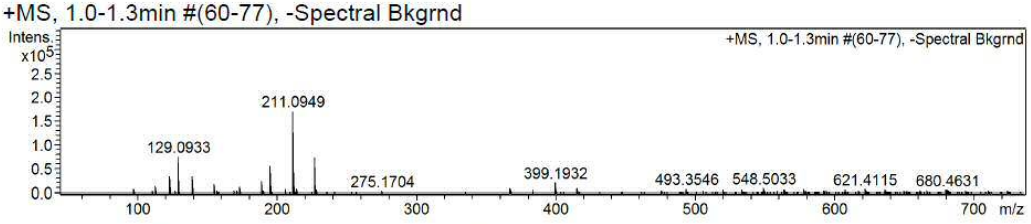

TJN135 HMBC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

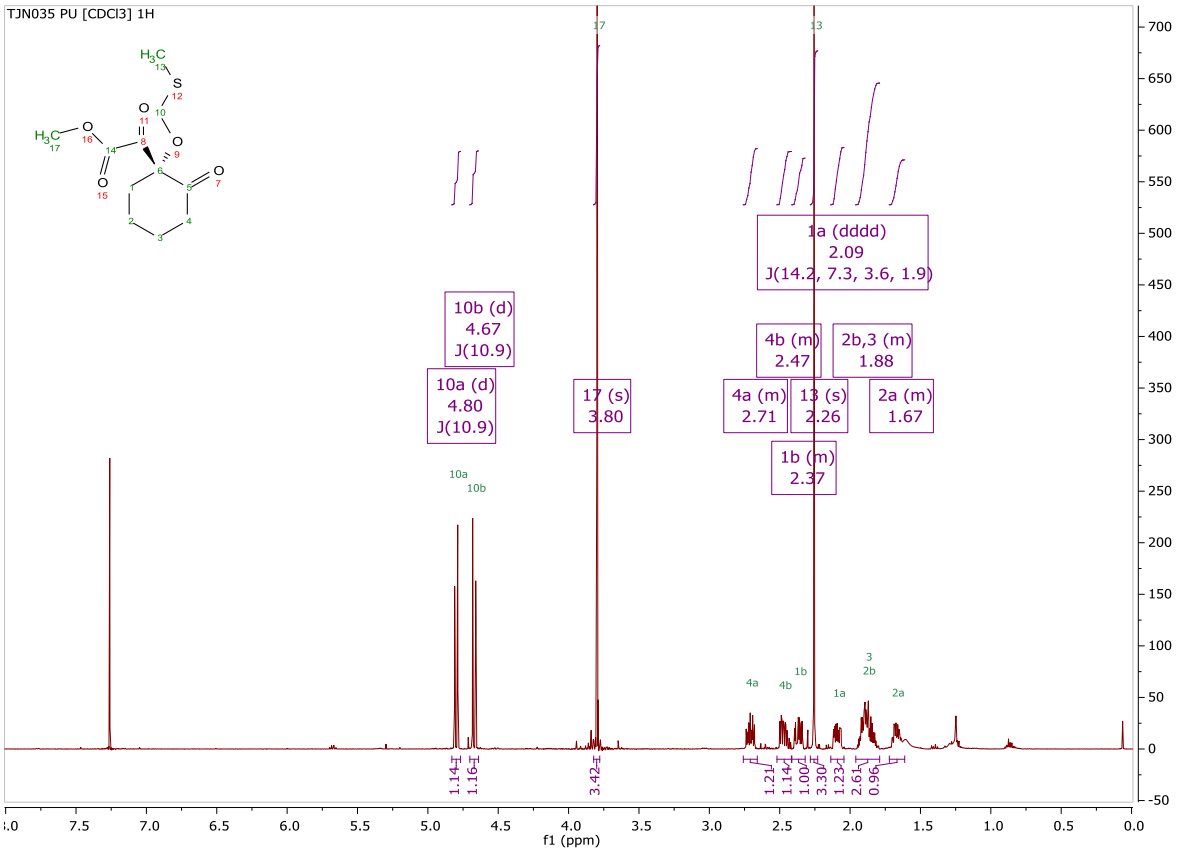
Sample-ID	tn_sel_TJN093	Submitter	Toby Nash
Analysis Name	tn_sel_TJN093_344768_25_01_49290.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	26/08/2015 09:20:04
Ionisation Mode	positive electrospray (ESI)		

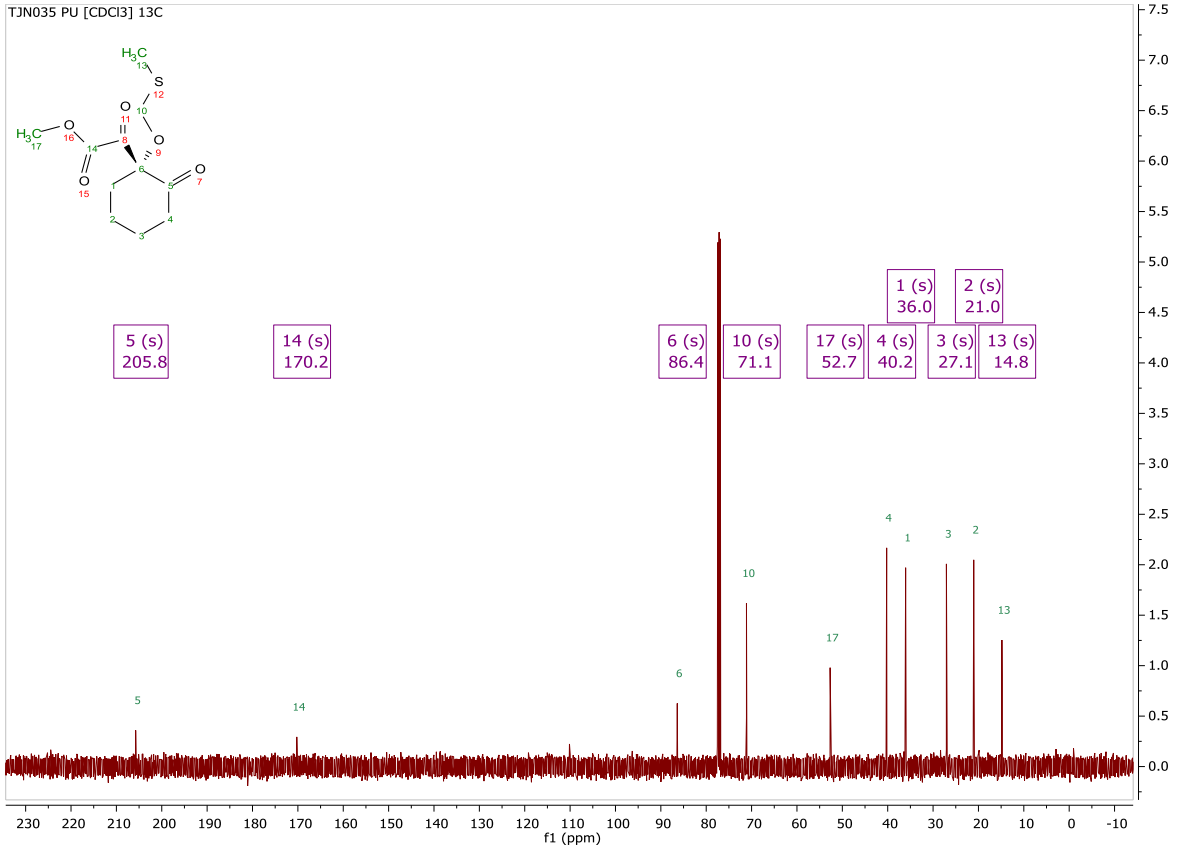
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

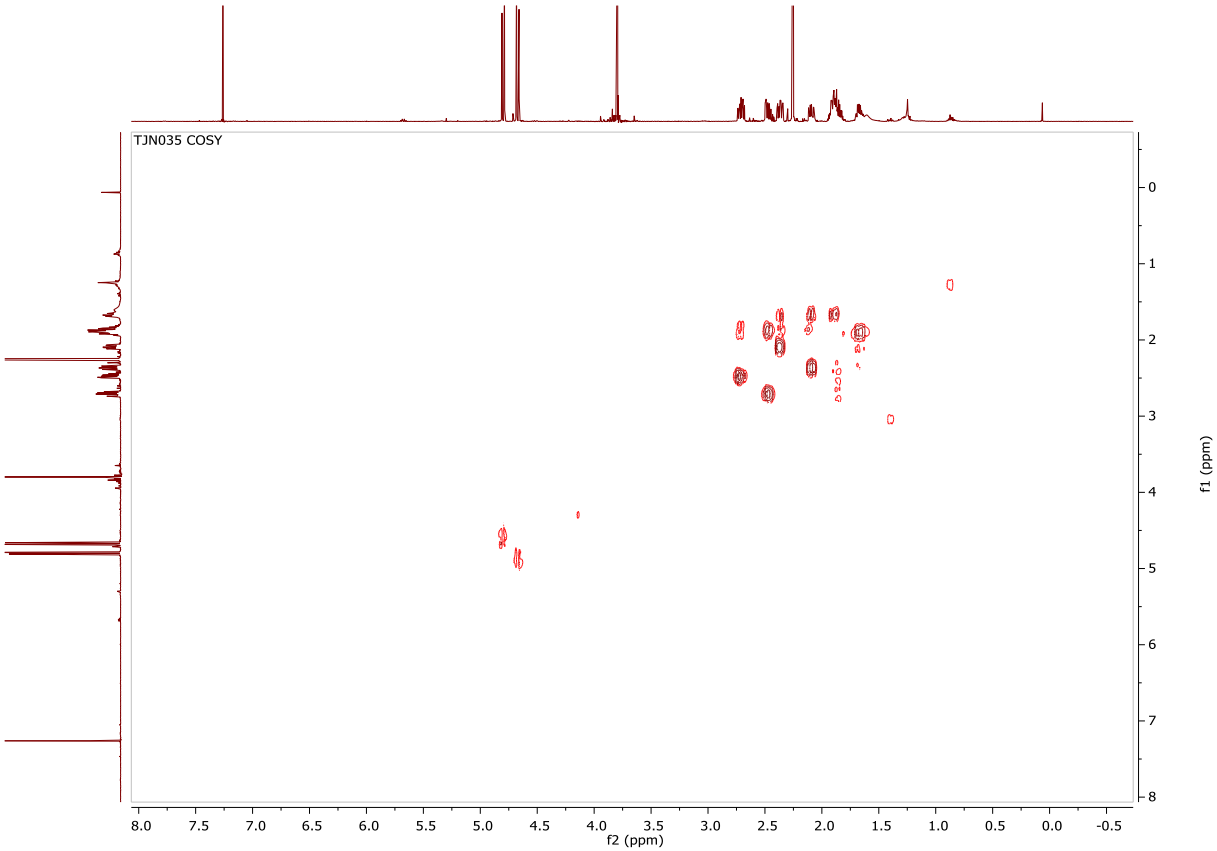


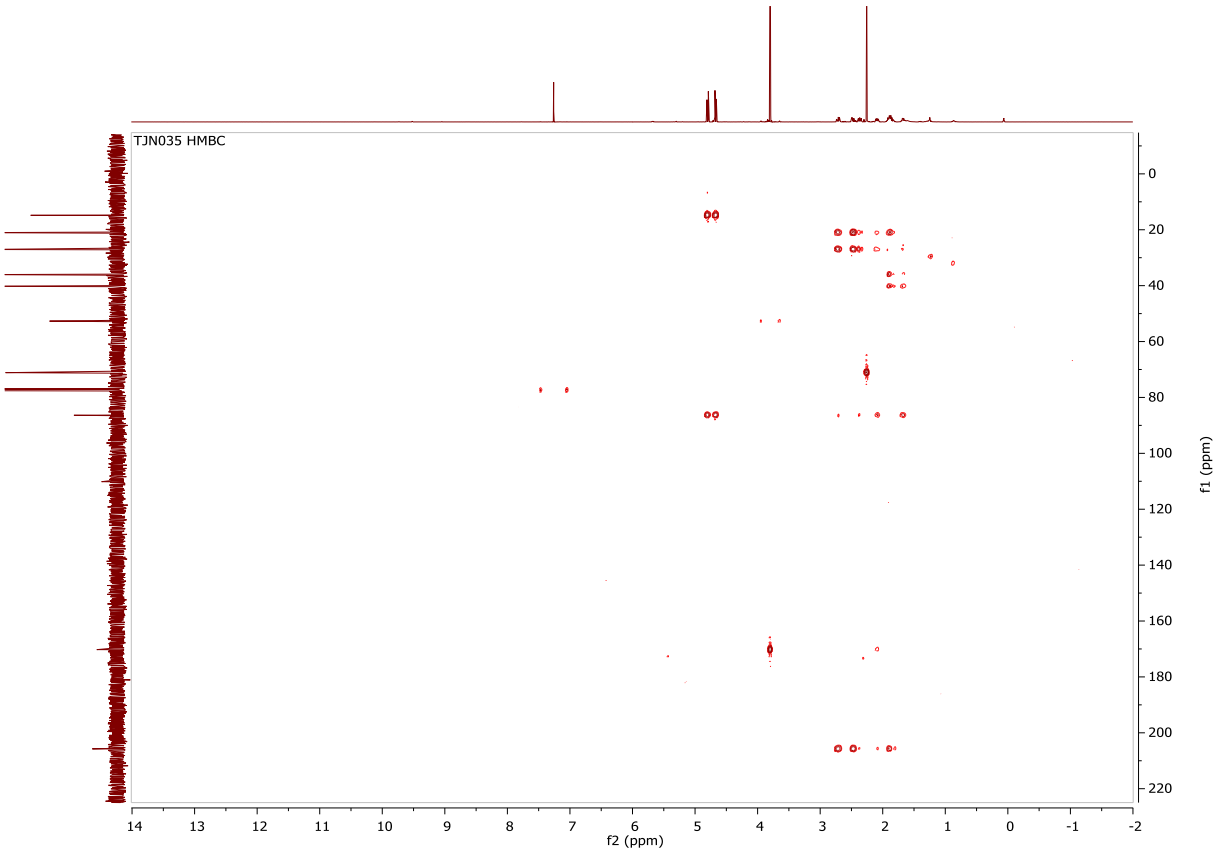
#	m/z	I	I %	Area	S/N
1	123.0460	33504	19.6	629	4007.8
2	129.0933	76078	44.5	1893	8818.2
3	139.0774	33836	19.8	910	3730.9
4	155.0719	18837	11.0	587	1926.6
5	189.1109	24859	14.5	750	893.6
6	195.0610	56213	32.9	1898	1787.3
7	211.0949	171032	100.0	6330	4916.5
8	212.0979	18326	10.7	787	536.7
9	227.0881	72795	42.6	3205	2968.7
10	399.1932	22390	13.1	2119	734.9

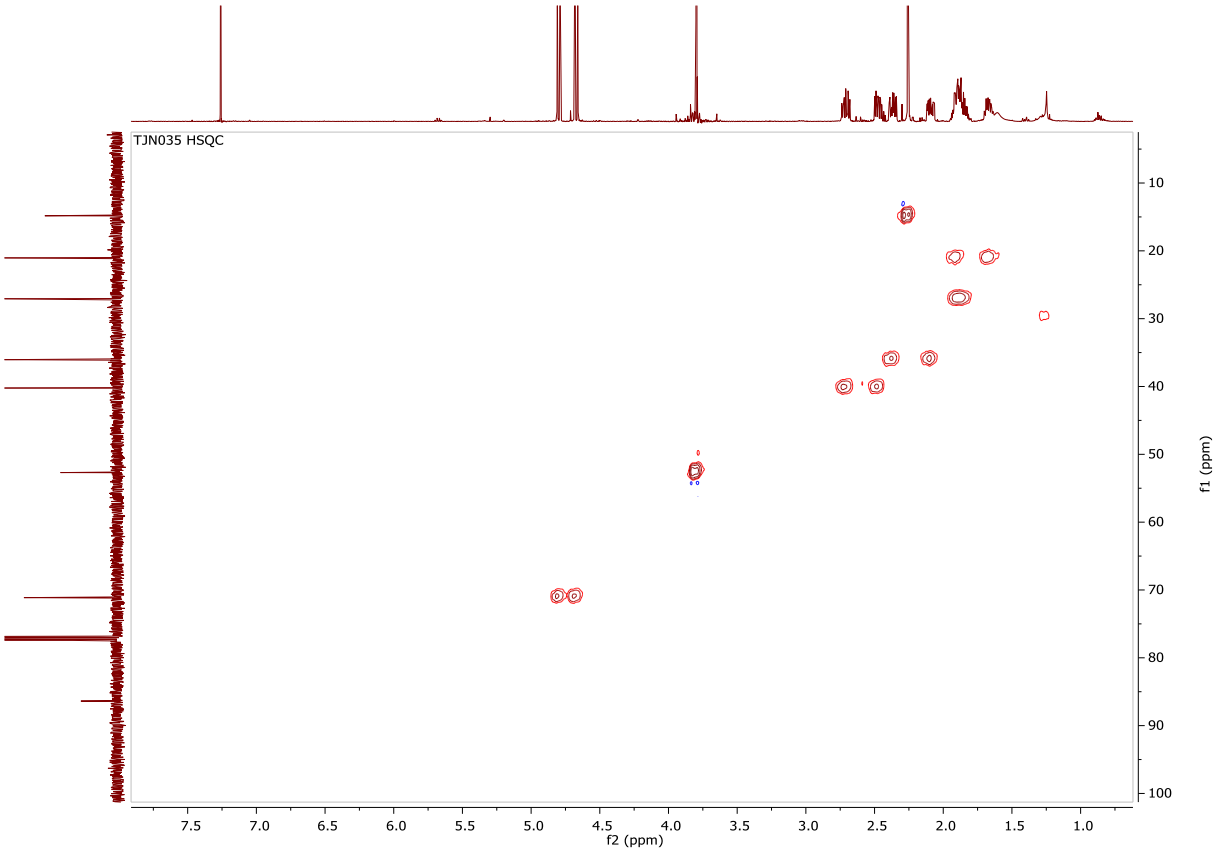
Methyl (*S*)-1-((methylthio)methoxy)-2-oxocyclohexane-1-carboxylate II-26






TJN035 COSY
f2 (ppm)
f1 (ppm)

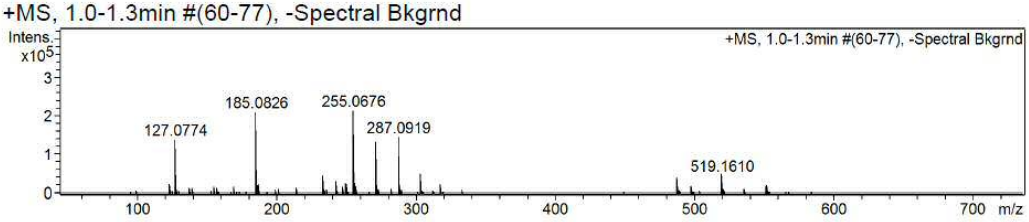

TJN035 HMBC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

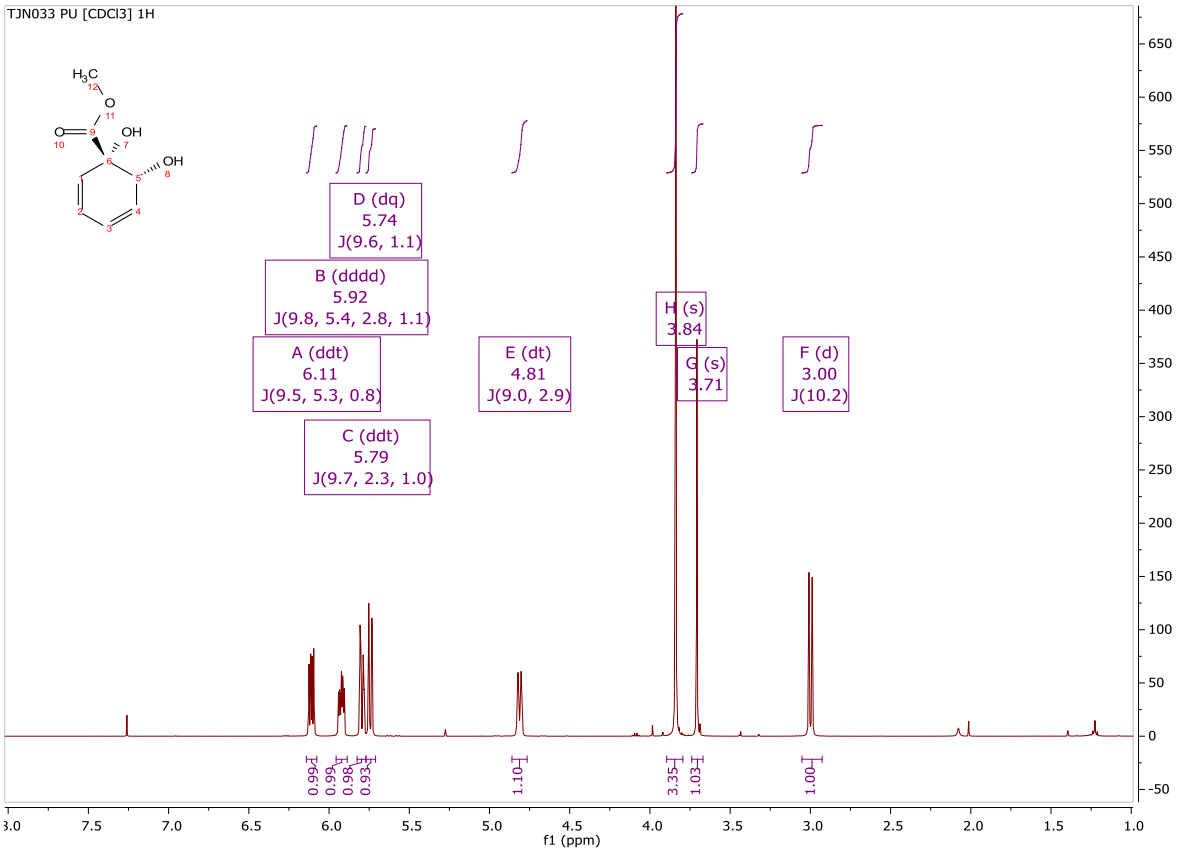
Sample-ID	tn_sel_TJN043	Submitter	Toby Nash
Analysis Name	tn_sel_TJN043_344756_13_01_49278.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	25/08/2015 09:18:29
Ionisation Mode	positive electrospray (ESI)		

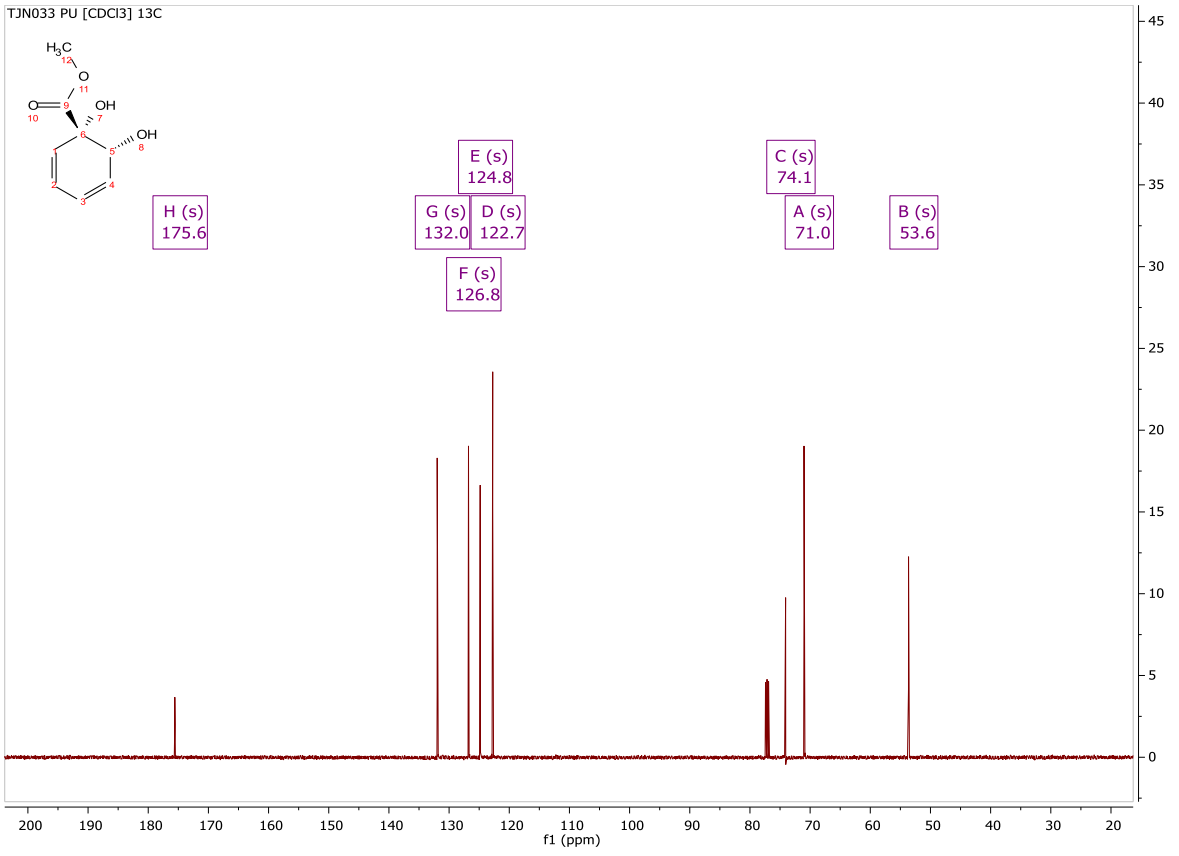
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



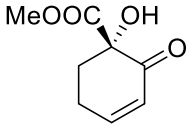
#	m/z	I	I %	Area	S/N
1	127.0774	138358	65.1	3289	10573.0
2	185.0826	209027	98.4	6691	9688.3
3	233.0840	45448	21.4	2047	722.4
4	242.2832	30770	14.5	1527	410.9
5	255.0676	212428	100.0	8770	2506.2
6	271.0614	133281	62.7	7053	1880.8
7	287.0919	144068	67.8	7326	2530.3
8	303.0855	48858	23.0	3008	1127.8
9	487.1458	40019	18.8	4088	1594.4
10	519.1610	45441	21.4	5695	1361.9

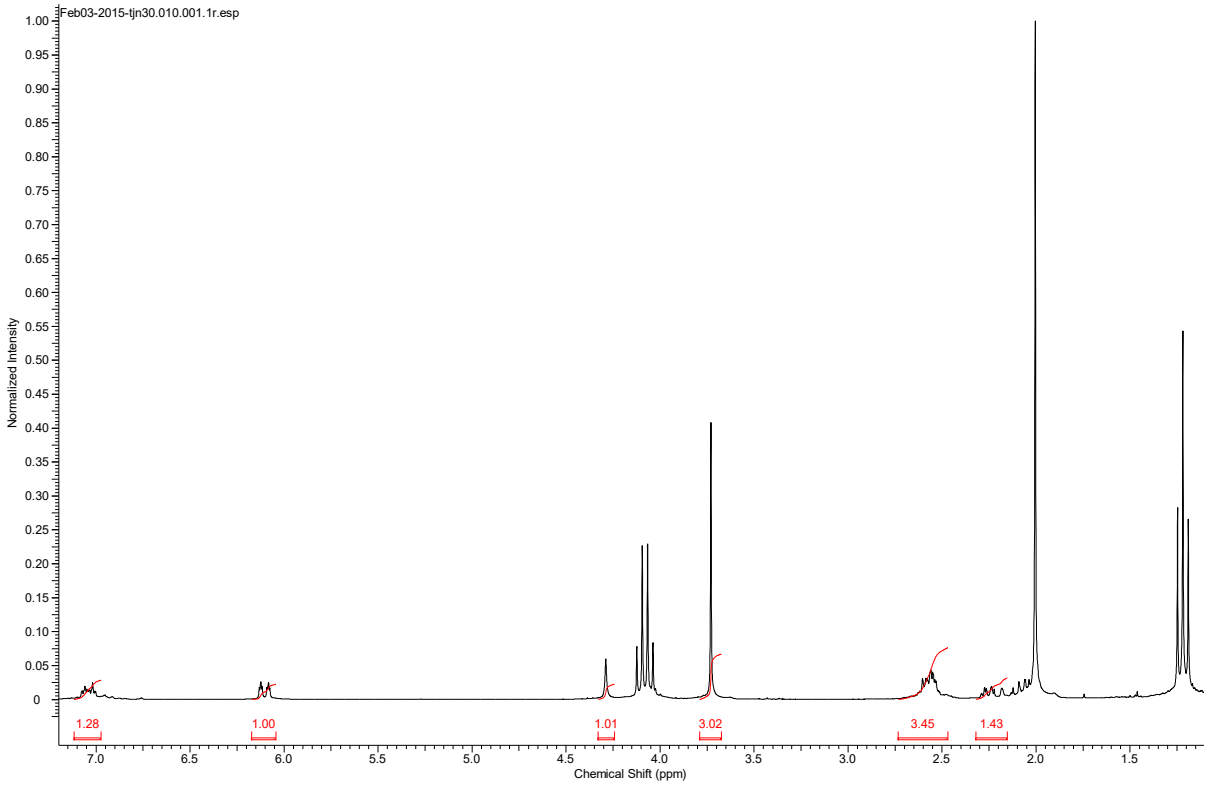
Methyl (1*S*,6*R*)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate II-27



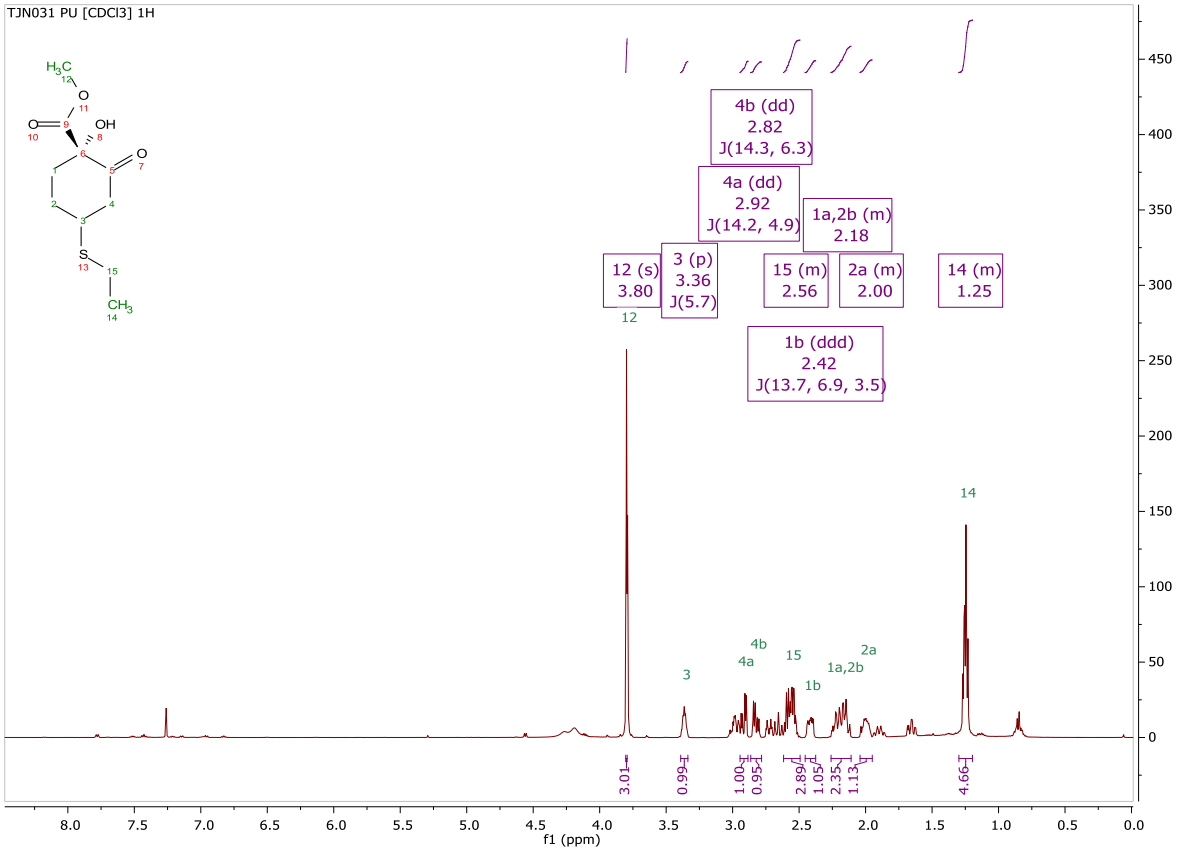


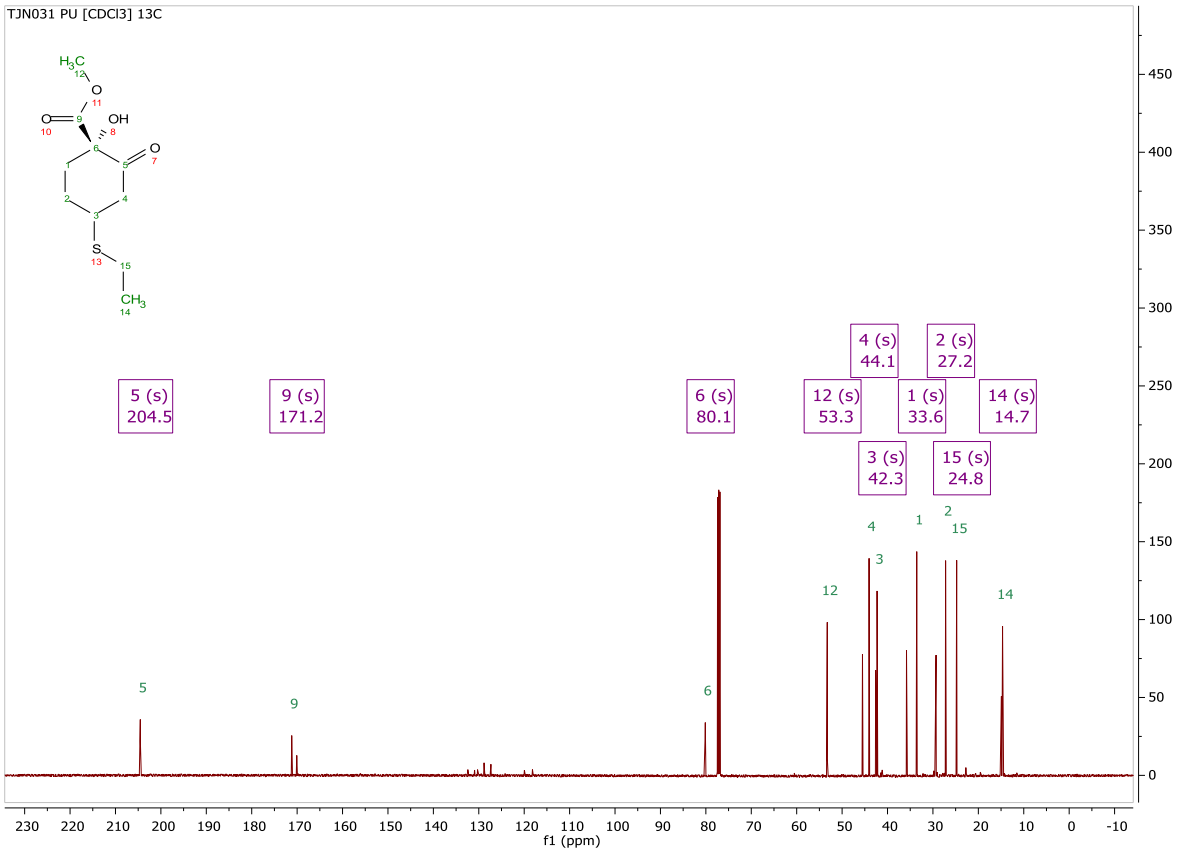
Methyl (*S*)-1-hydroxy-2-oxocyclohex-3-ene-1-carboxylate II-28

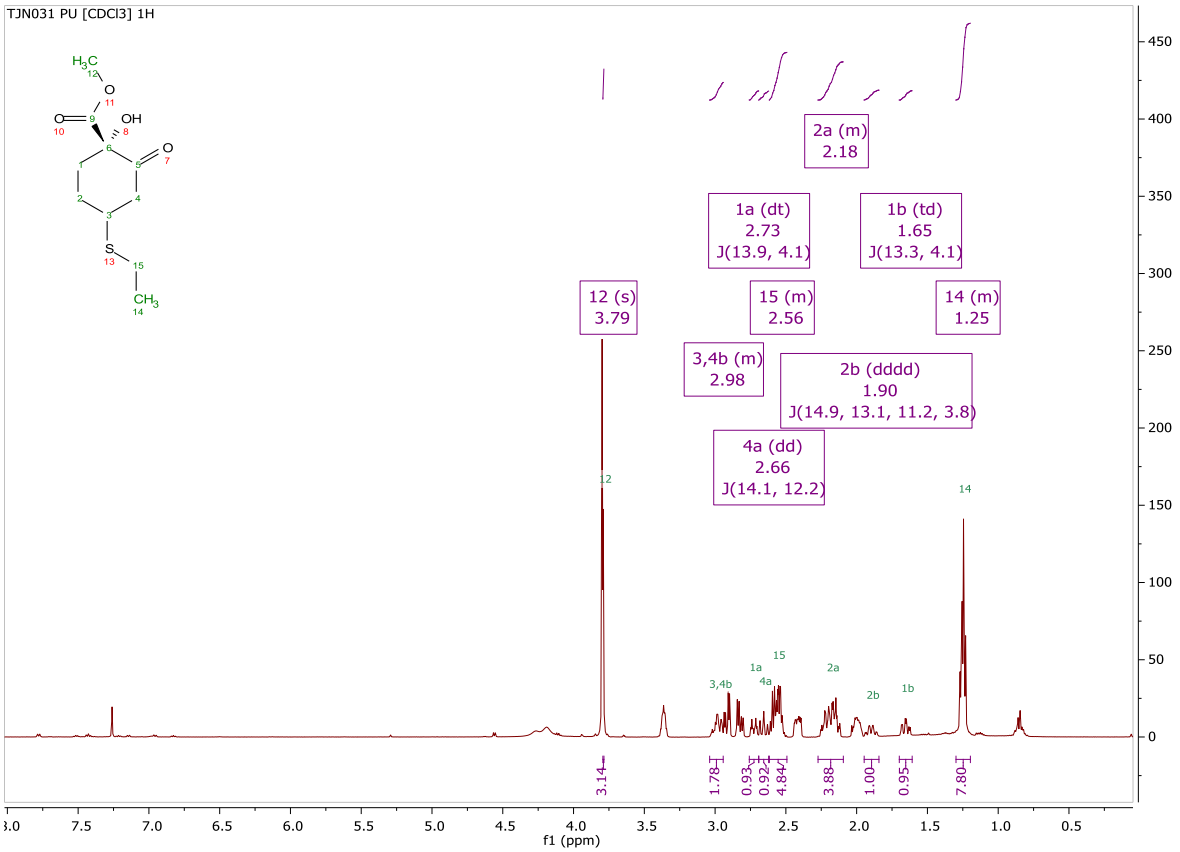


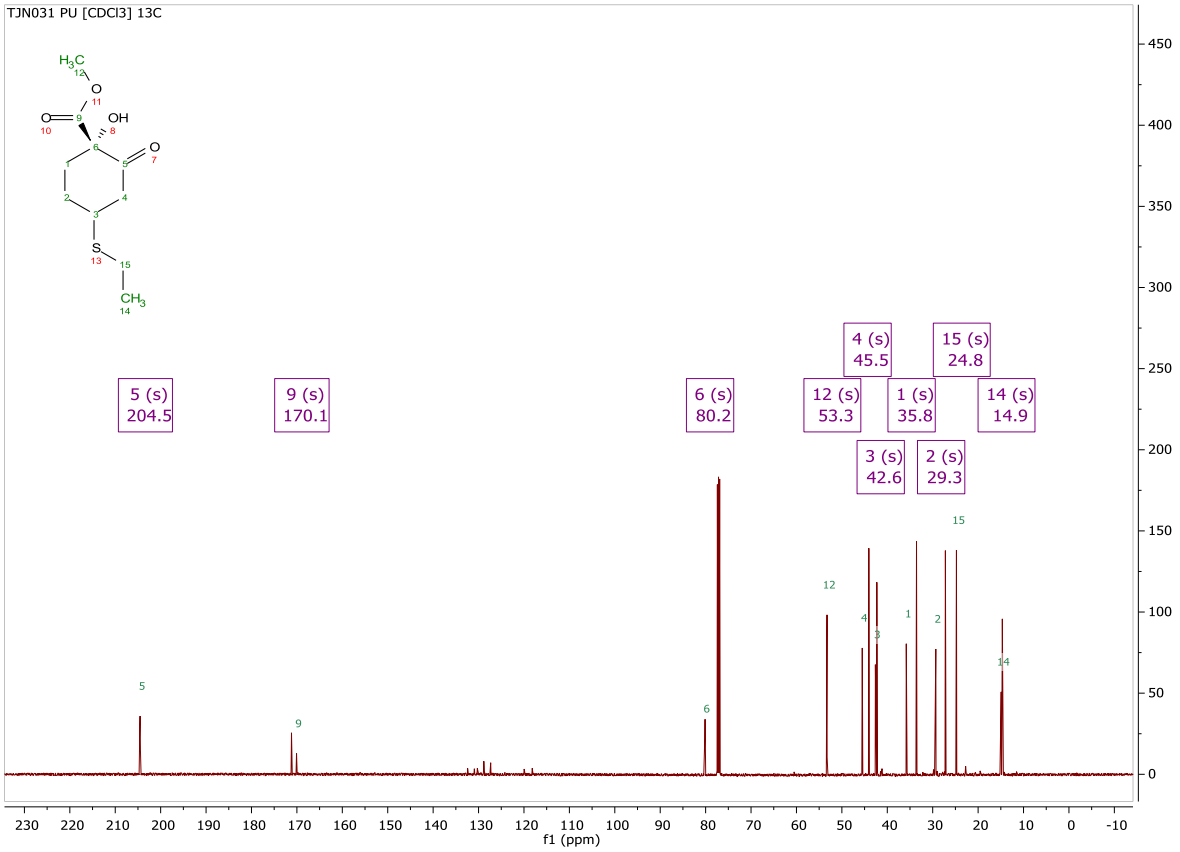


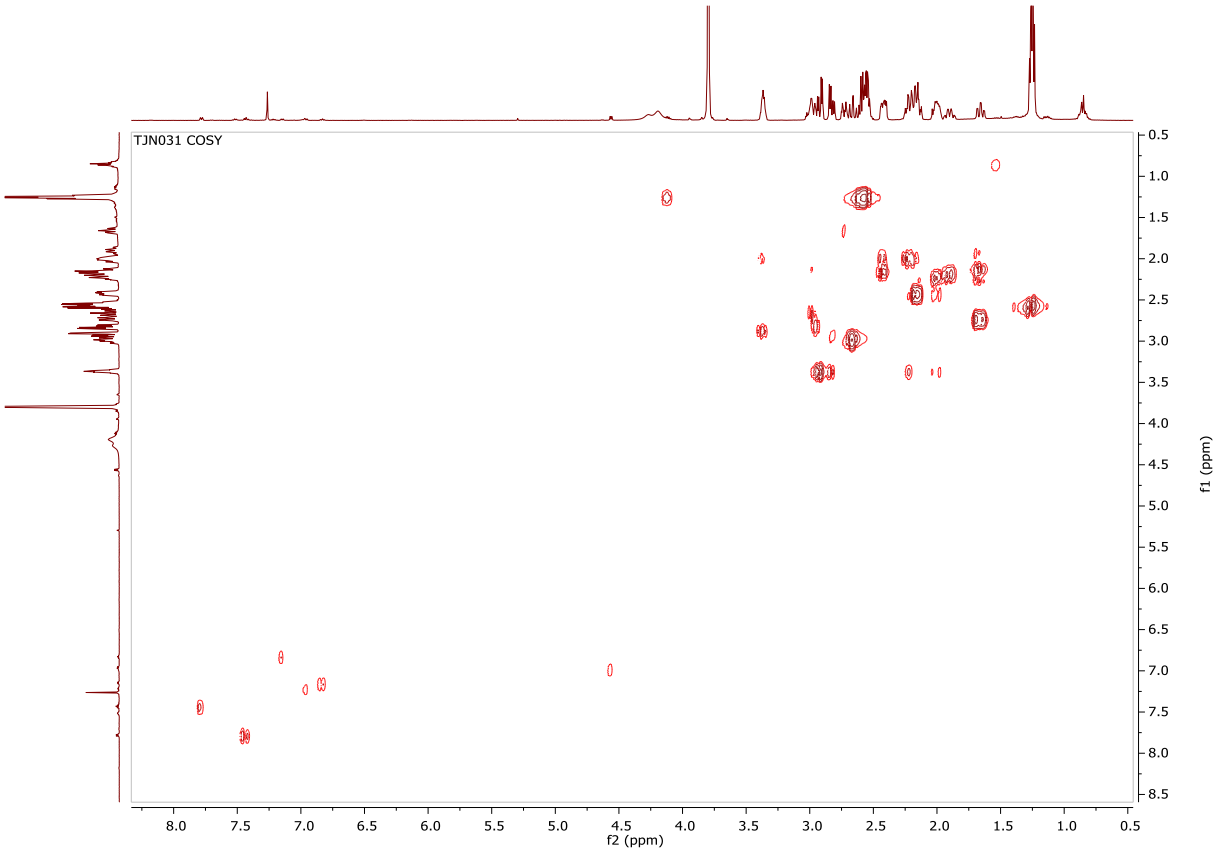
Methyl (1*S*)-4-(ethylthio)-1-hydroxy-2-oxocyclohexane-1-carboxylate II-29

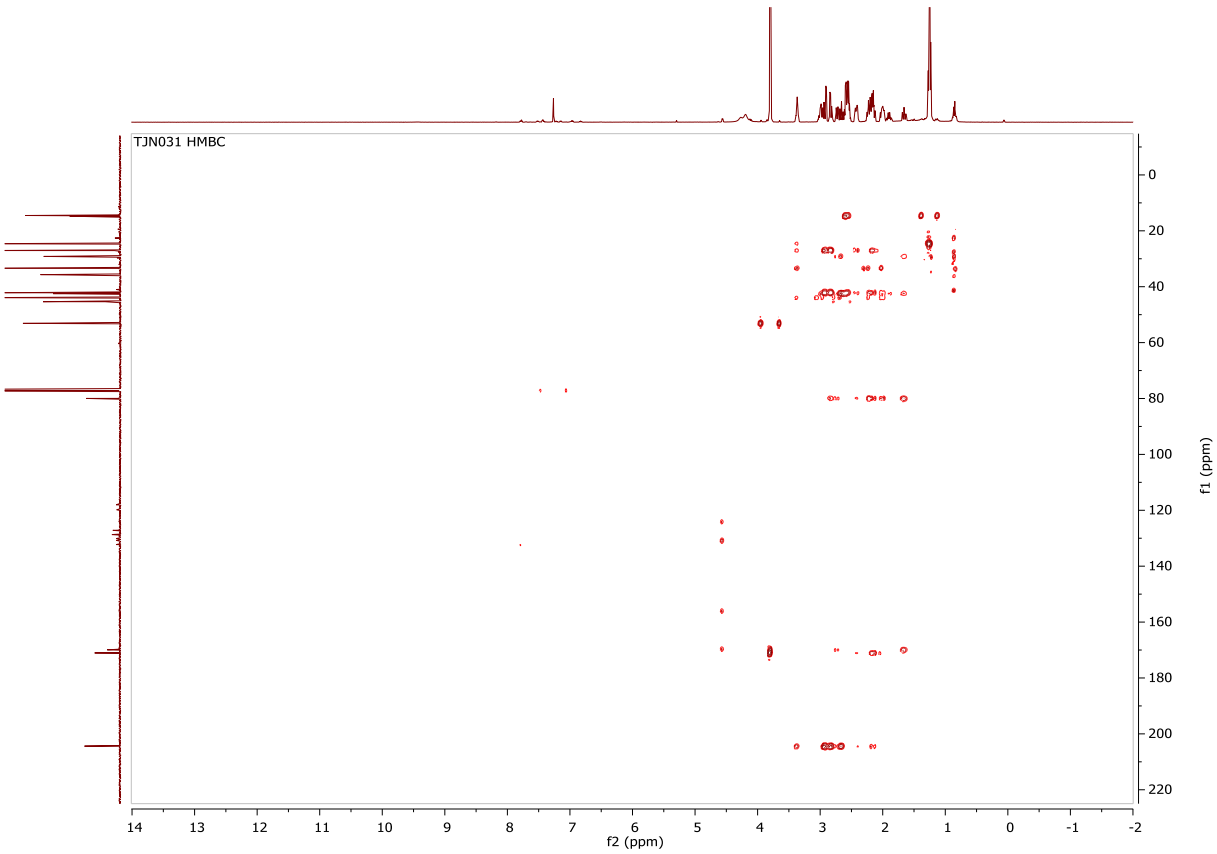


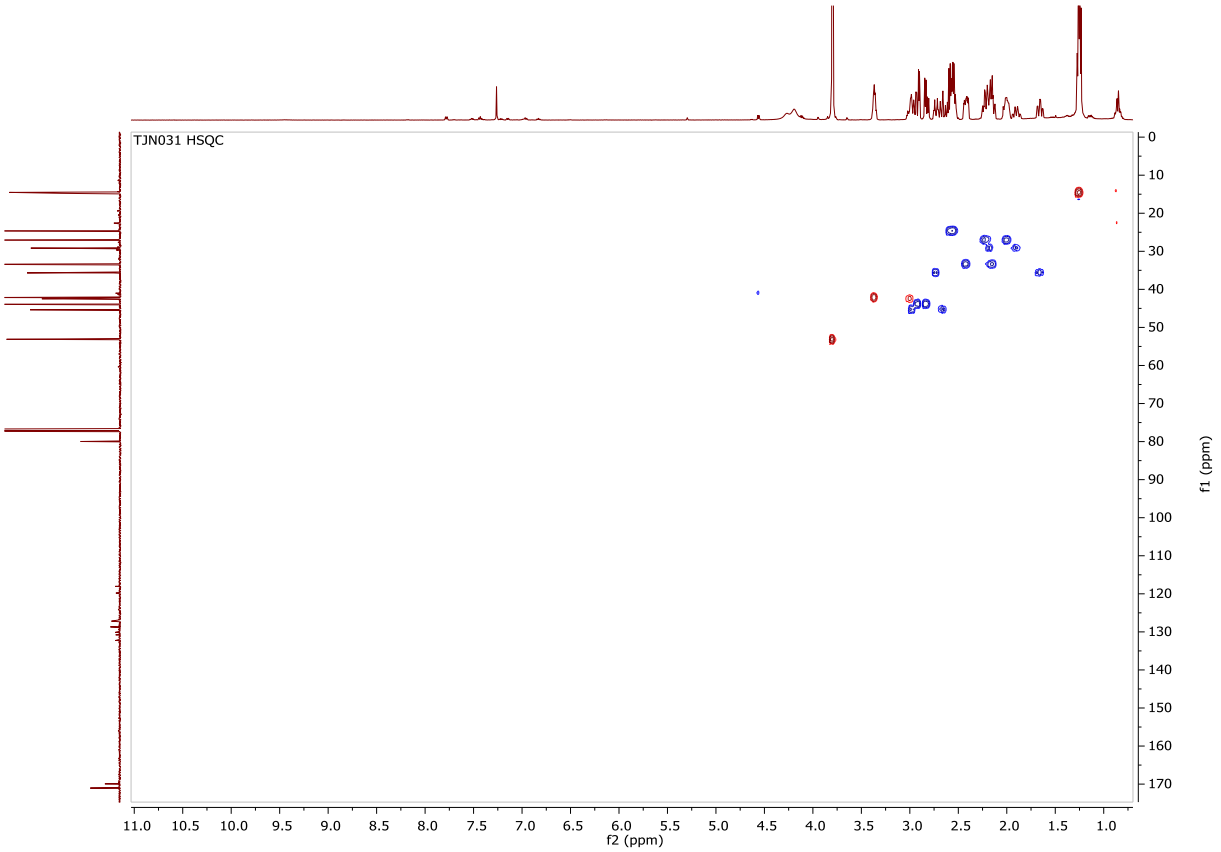



TJN031 PU [CDCl3] 1H
2a (m)
2.18
1a (dt)
2.73
J(13.9, 4.1)
1b (td)
1.65
J(13.3, 4.1)
12 (s)
3.79
15 (m)
2.56
14 (m)
1.25
3,4b (m)
2.98
2b (dddd)
1.90
J(14.9, 13.1, 11.2, 3.8)
4a (dd)
2.66
J(14.1, 12.2)
3.14
1.78
0.93
0.92
4.84
3.88
1.00
0.95
7.80
f1 (ppm)


TJN031 PU [CDCl3] 13C
5 (s)
204.5
9 (s)
170.1
6 (s)
80.2
4 (s)
45.5
15 (s)
24.8
12 (s)
53.3
1 (s)
35.8
14 (s)
14.9
3 (s)
42.6
2 (s)
29.3
f1 (ppm)


TJN031 COSY
f2 (ppm)
f1 (ppm)

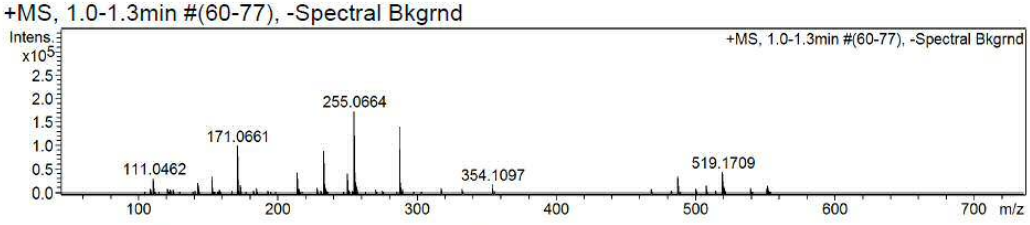

TJN031 HMBC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

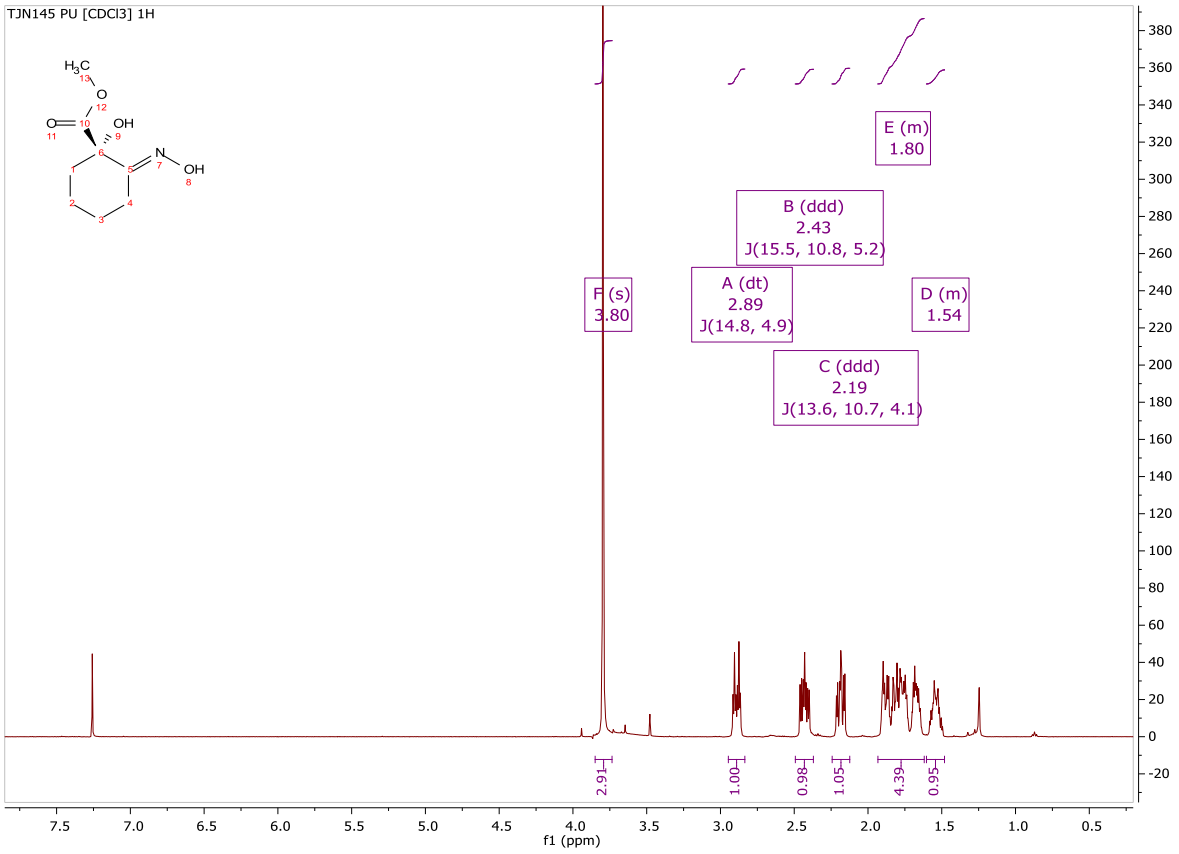
Sample-ID	tn_sel_TJN031	Submitter	Toby Nash
Analysis Name	tn_sel_TJN031_344767_24_01_49289.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	26/08/2015 09:16:20
Ionisation Mode	positive electrospray (ESI)		

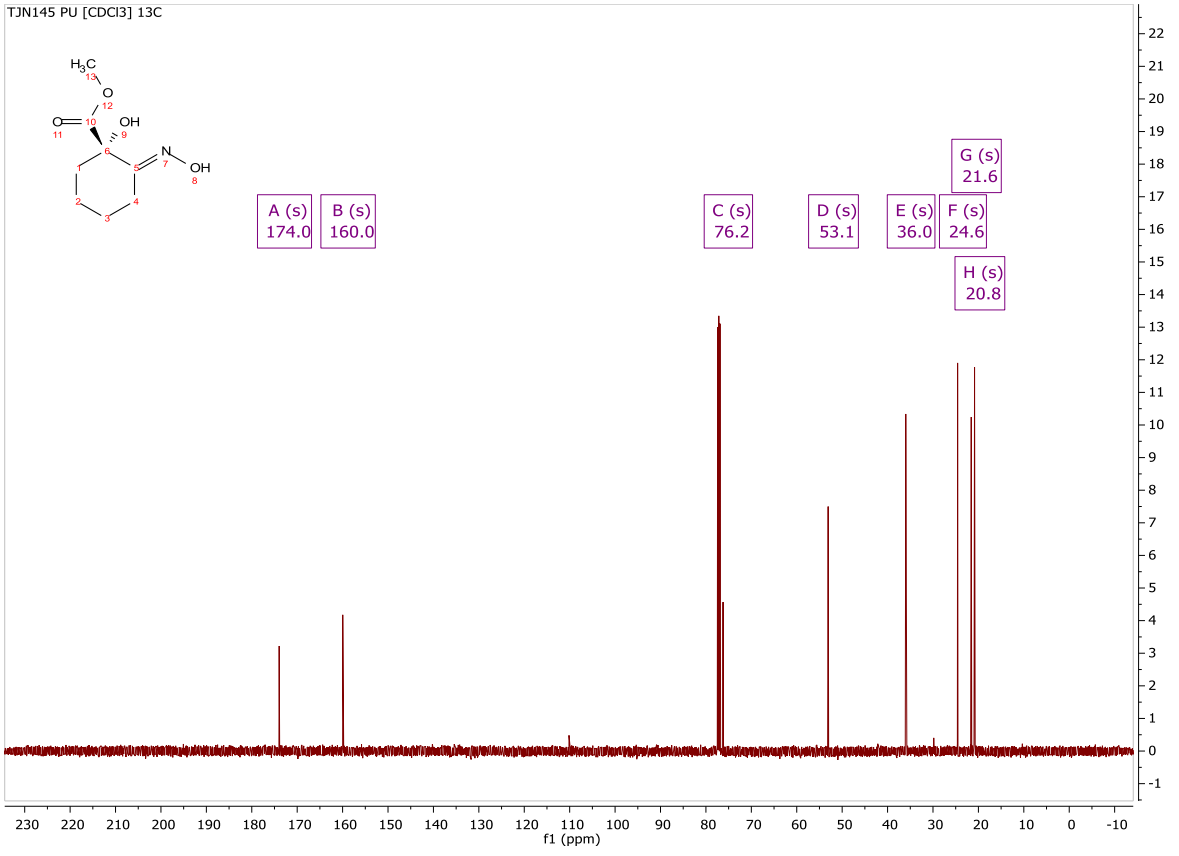
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	111.0462	31374	18.1	732	3538.6
2	153.0565	34921	20.1	1040	1623.6
3	171.0661	100410	57.9	3241	4287.5
4	214.0931	42608	24.5	680	1416.5
5	233.0840	89536	51.6	3828	1901.3
6	250.1051	40608	23.4	2332	651.4
7	255.0664	173566	100.0	7415	2807.8
8	287.0918	140513	81.0	7153	3571.4
9	487.1471	34055	19.6	3621	950.8
10	519.1709	44294	25.5	5066	983.1

Methyl (*S*,*E*)-1-hydroxy-2-(hydroxyimino)cyclohexane-1-carboxylate II-30





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Results of job 77345

Sample	Sample Description	Method	Submitter	Pos	Expected Formula	Project	Peaknumber	meas. m/z	theo. m/z	err[ppm]	sigma	Formulae
tn_sel_TJN145		Confirm Formula Positive 50to500 loop inj	tjn30 Toby Nash		C8 H13 N1 O4	TJN145	1	188.092700	188.0917	5	0.0061	C 8 H 14 N 1 O 4

Crystal structure data for II-30

Table 1. Crystal data and structure refinement for s15sel3.

Identification code	s15sel3	
Empirical formula	C8 H13 N O4	
Formula weight	187.19	
Temperature	150(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 6.87780(10) Å	α= 90°.
	b = 9.14210(10) Å	β= 108.648(2)°.
	c = 7.55690(10) Å	γ = 90°.
Volume	450.214(11) $Å^3$	
Z	2	
Density (calculated)	1.381 Mg/m^3	
Absorption coefficient	0.940 mm^{-1}	
F(000)	200	
Crystal size	0.400 x 0.200 x 0.100 mm^3	
Theta range for data collection	6.181 to 72.443°.	
Index ranges	-8<=h<=8, -11<=k<=9, -9<=l<=9	
Reflections collected	5256	
Independent reflections	1501 [R(int) = 0.0202]	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.69487	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1501 / 1 / 125	
Goodness-of-fit on F^2	1.113	
Final R indices [I>2sigma(I)]	R1 = 0.0256, wR2 = 0.0661	
R indices (all data)	R1 = 0.0258, wR2 = 0.0663	
Absolute structure parameter	-0.02(11)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.138 and -0.184 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for s15sel3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N	6174(2)	6666(2)	7381(2)	19(1)
O(1)	6344(2)	3698(2)	5510(2)	22(1)
O(2)	7533(2)	7640(2)	8620(2)	26(1)
O(3)	2657(2)	4930(2)	3658(2)	27(1)
O(4)	2025(2)	5464(2)	6296(2)	28(1)
C(1)	5148(3)	4207(2)	6606(2)	19(1)
C(2)	6495(2)	5345(2)	7914(2)	19(1)
C(3)	8160(3)	4809(2)	9613(2)	28(1)
C(4)	7409(3)	3587(2)	10613(2)	28(1)
C(5)	6439(3)	2365(2)	9253(2)	27(1)
C(6)	4579(3)	2944(2)	7705(2)	24(1)
C(7)	3163(3)	4915(2)	5340(2)	20(1)
C(8)	104(3)	6124(3)	5182(3)	31(1)

Table 3. Bond lengths [Å] for s15sel3.

N-C(2)	1.271(2)
N-O(2)	1.4084(19)
O(1)-C(1)	1.4198(19)
O(1)-H(1)	0.83(3)
O(2)-H(2)	0.87(3)
O(3)-C(7)	1.206(2)
O(4)-C(7)	1.322(2)
O(4)-C(8)	1.452(2)
C(1)-C(2)	1.527(2)
C(1)-C(7)	1.537(2)
C(1)-C(6)	1.544(2)
C(2)-C(3)	1.503(2)
C(3)-C(4)	1.528(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.520(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.526(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800

Table 4. Bond angles [°] for s15sel3.

C(2)-N-O(2)	112.29(14)
C(1)-O(1)-H(1)	109.8(17)
N-O(2)-H(2)	105.4(18)
C(7)-O(4)-C(8)	115.41(14)
O(1)-C(1)-C(2)	104.83(13)
O(1)-C(1)-C(7)	109.87(13)
C(2)-C(1)-C(7)	110.52(14)
O(1)-C(1)-C(6)	111.25(14)
C(2)-C(1)-C(6)	111.52(14)
C(7)-C(1)-C(6)	108.81(14)
N-C(2)-C(3)	126.05(16)
N-C(2)-C(1)	115.75(14)
C(3)-C(2)-C(1)	118.02(15)
C(2)-C(3)-C(4)	112.03(14)
C(2)-C(3)-H(3A)	109.2
C(4)-C(3)-H(3A)	109.2
C(2)-C(3)-H(3B)	109.2
C(4)-C(3)-H(3B)	109.2
H(3A)-C(3)-H(3B)	107.9
C(5)-C(4)-C(3)	110.35(15)
C(5)-C(4)-H(4A)	109.6
C(3)-C(4)-H(4A)	109.6
C(5)-C(4)-H(4B)	109.6
C(3)-C(4)-H(4B)	109.6
H(4A)-C(4)-H(4B)	108.1
C(4)-C(5)-C(6)	110.01(15)
C(4)-C(5)-H(5A)	109.7
C(6)-C(5)-H(5A)	109.7
C(4)-C(5)-H(5B)	109.7
C(6)-C(5)-H(5B)	109.7
H(5A)-C(5)-H(5B)	108.2
C(5)-C(6)-C(1)	112.20(15)
C(5)-C(6)-H(6A)	109.2
C(1)-C(6)-H(6A)	109.2
C(5)-C(6)-H(6B)	109.2
C(1)-C(6)-H(6B)	109.2
H(6A)-C(6)-H(6B)	107.9

O(3)-C(7)-O(4)	123.35(16)
O(3)-C(7)-C(1)	124.09(15)
O(4)-C(7)-C(1)	112.52(13)
O(4)-C(8)-H(8A)	109.5
O(4)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
O(4)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for s15sel3. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N	19(1)	20(1)	18(1)	-1(1)	6(1)	-3(1)
O(1)	21(1)	24(1)	23(1)	-4(1)	10(1)	0(1)
O(2)	31(1)	19(1)	24(1)	-1(1)	4(1)	-7(1)
O(3)	33(1)	24(1)	20(1)	-1(1)	4(1)	7(1)
O(4)	18(1)	41(1)	25(1)	-5(1)	6(1)	3(1)
C(1)	18(1)	20(1)	19(1)	0(1)	7(1)	-1(1)
C(2)	18(1)	22(1)	18(1)	1(1)	6(1)	0(1)
C(3)	24(1)	26(1)	26(1)	4(1)	-1(1)	-3(1)
C(4)	31(1)	27(1)	22(1)	6(1)	3(1)	0(1)
C(5)	34(1)	22(1)	25(1)	6(1)	10(1)	-2(1)
C(6)	26(1)	24(1)	24(1)	2(1)	9(1)	-6(1)
C(7)	20(1)	17(1)	22(1)	-3(1)	6(1)	-3(1)
C(8)	17(1)	37(1)	36(1)	-7(1)	4(1)	4(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for s15sel3.

	x	y	z	U(eq)
H(1)	5710(40)	3040(30)	4790(30)	33
H(2)	7320(40)	8480(30)	8060(30)	39
H(3A)	8662	5635	10487	33
H(3B)	9324	4444	9235	33
H(4A)	8578	3194	11642	33
H(4B)	6389	3984	11160	33
H(5A)	6009	1562	9926	32
H(5B)	7456	1969	8703	32
H(6A)	3540	3293	8260	29
H(6B)	3960	2137	6833	29
H(8A)	386	6936	4453	47
H(8B)	-632	6492	6007	47
H(8C)	-739	5389	4333	47

Table 7. Torsion angles [°] for s15sel3.

O(2)-N-C(2)-C(3)	-2.4(2)
O(2)-N-C(2)-C(1)	-177.46(13)
O(1)-C(1)-C(2)-N	95.90(16)
C(7)-C(1)-C(2)-N	-22.43(19)
C(6)-C(1)-C(2)-N	-143.62(15)
O(1)-C(1)-C(2)-C(3)	-79.59(17)
C(7)-C(1)-C(2)-C(3)	162.08(14)
C(6)-C(1)-C(2)-C(3)	40.9(2)
N-C(2)-C(3)-C(4)	140.66(18)
C(1)-C(2)-C(3)-C(4)	-44.4(2)
C(2)-C(3)-C(4)-C(5)	53.4(2)
C(3)-C(4)-C(5)-C(6)	-61.6(2)
C(4)-C(5)-C(6)-C(1)	59.05(19)
O(1)-C(1)-C(6)-C(5)	69.41(18)
C(2)-C(1)-C(6)-C(5)	-47.2(2)
C(7)-C(1)-C(6)-C(5)	-169.40(14)
C(8)-O(4)-C(7)-O(3)	-1.0(3)
C(8)-O(4)-C(7)-C(1)	-178.78(16)
O(1)-C(1)-C(7)-O(3)	4.9(2)
C(2)-C(1)-C(7)-O(3)	120.11(19)
C(6)-C(1)-C(7)-O(3)	-117.11(19)
O(1)-C(1)-C(7)-O(4)	-177.38(15)
C(2)-C(1)-C(7)-O(4)	-62.18(18)
C(6)-C(1)-C(7)-O(4)	60.60(19)

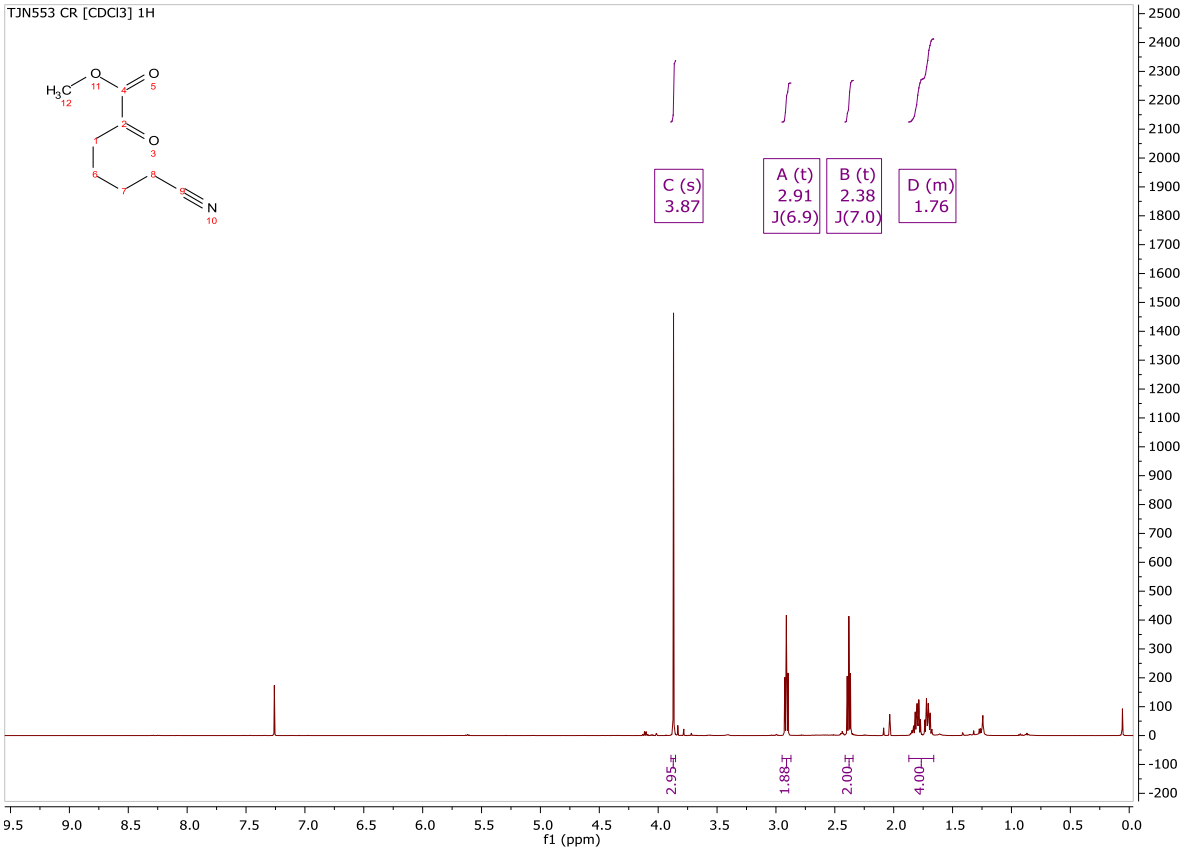
Table 8. Hydrogen bonds for s15sel3 [Å and °].

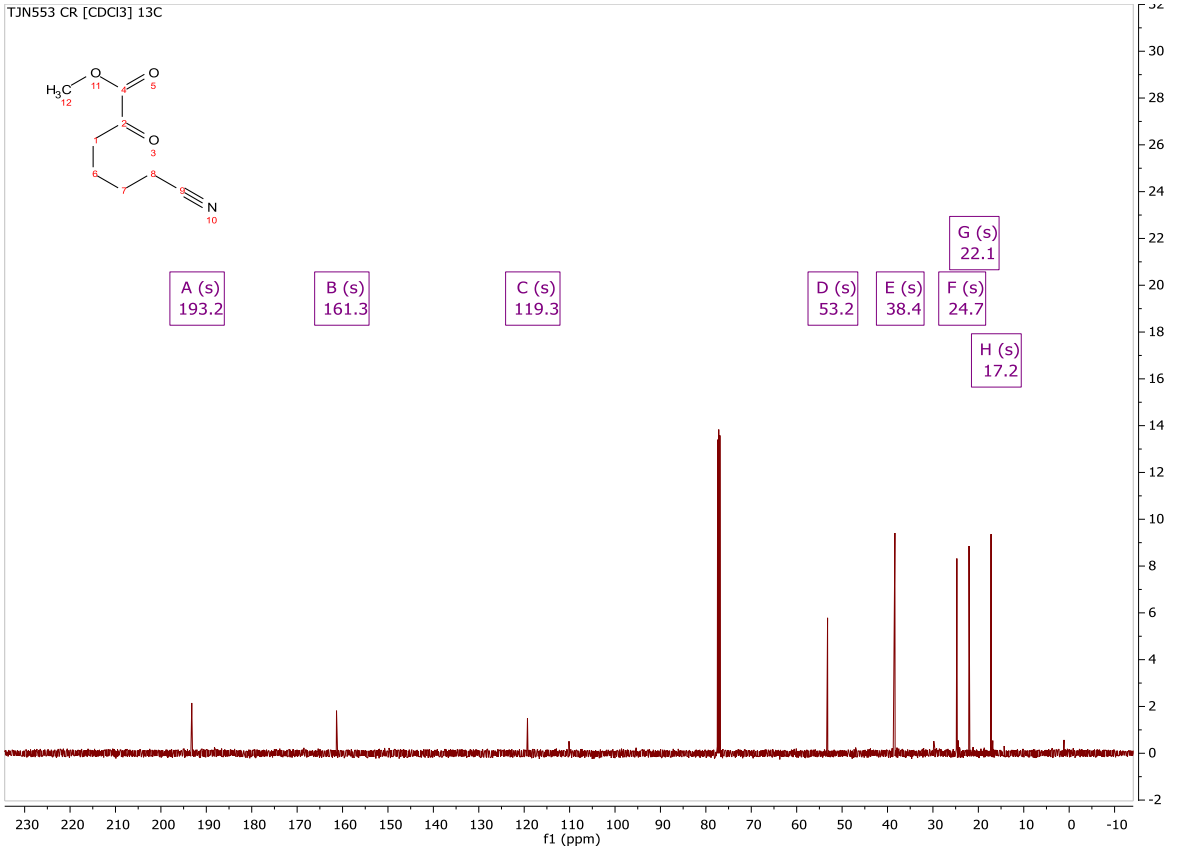
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...N#1	0.83(3)	2.14(3)	2.967(2)	170(2)
O(2)-H(2)...O(3)#2	0.87(3)	1.86(3)	2.6866(18)	159(3)

Symmetry transformations used to generate equivalent atoms:

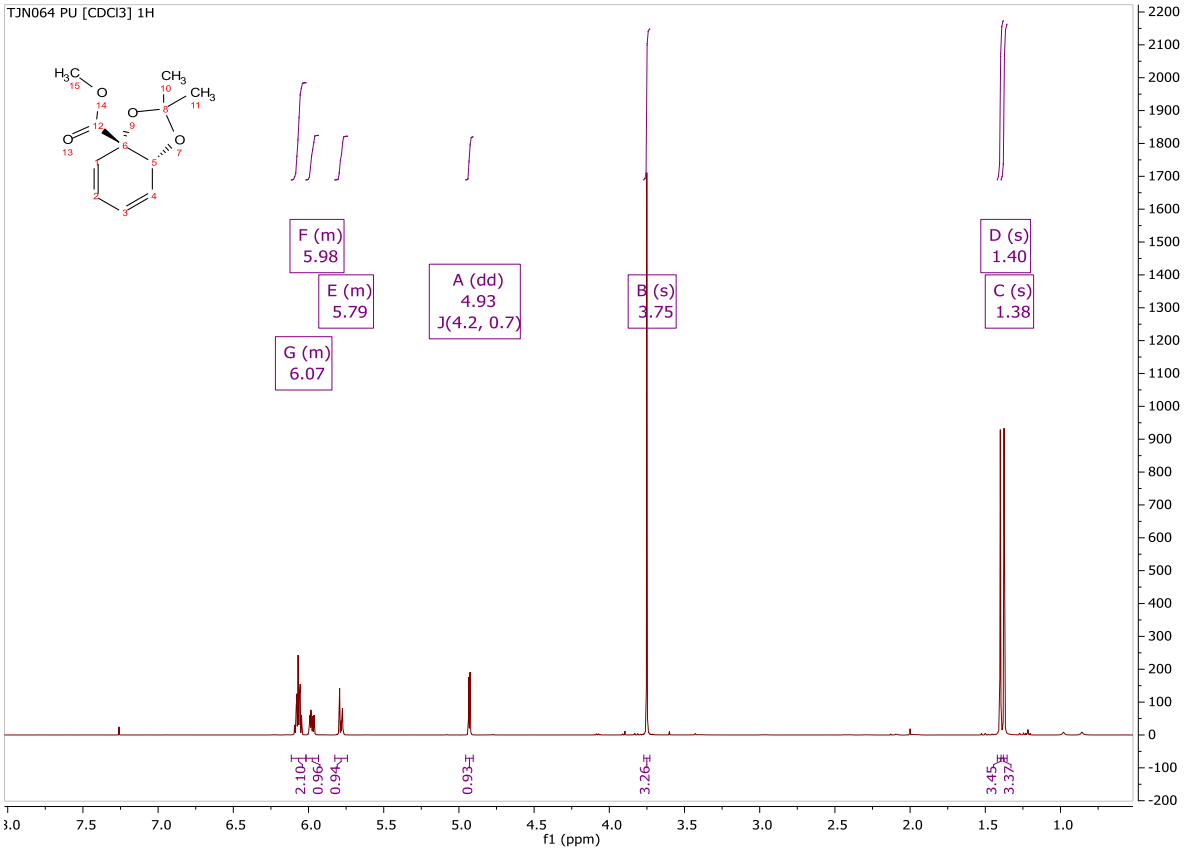
#1 -x+1,y-1/2,-z+1 #2 -x+1,y+1/2,-z+1

Methyl 6-cyano-2-oxohexanoate II-32





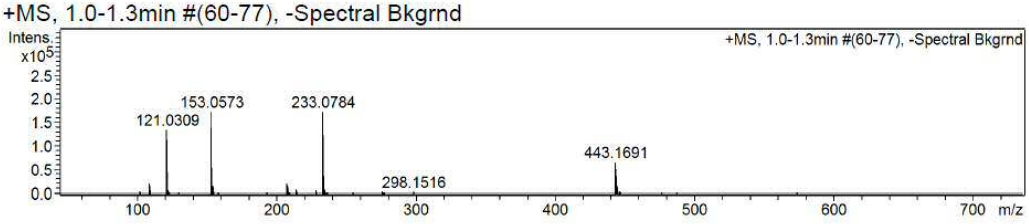
Methyl (3a*S*,7a*R*)-2,2-dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylate II-13



Confirmation of Expected Formula

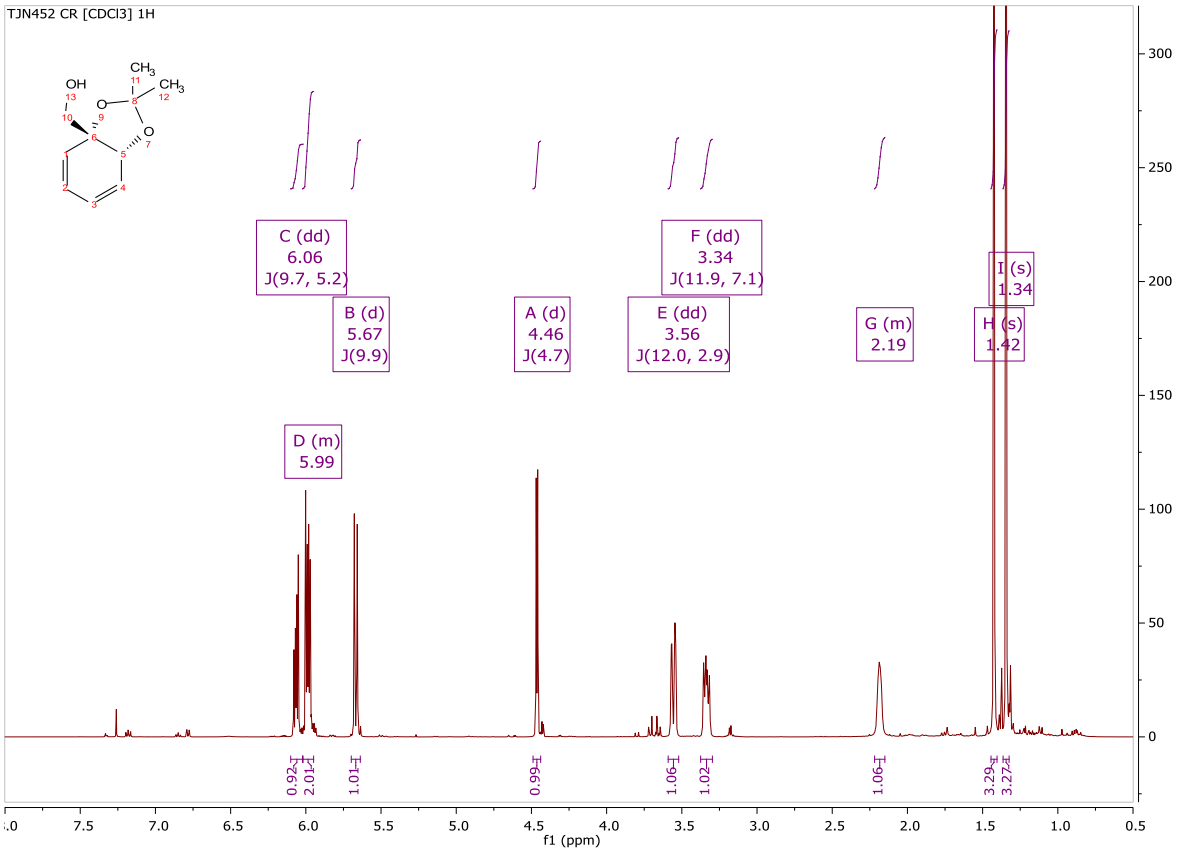
Sample-ID	tn_sel_tjn064	Submitter	Toby Nash
Analysis Name	tn_sel_tjn064_343890_30_01_48305.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	27/05/2015 12:30:28
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	109.0669	20282	11.7	449	2977.8
2	121.0309	134450	77.7	2811	15715.1
3	153.0573	172560	99.7	4524	13434.0
4	154.0601	15959	9.2	475	1229.6
5	207.0633	20967	12.1	909	1776.3
6	208.1839	16545	9.6	344	1348.1
7	233.0784	173017	100.0	6448	7623.3
8	234.0845	9381	5.4	408	405.8
9	443.1691	66514	38.4	5268	3282.1
10	444.1718	14064	8.1	1403	699.4

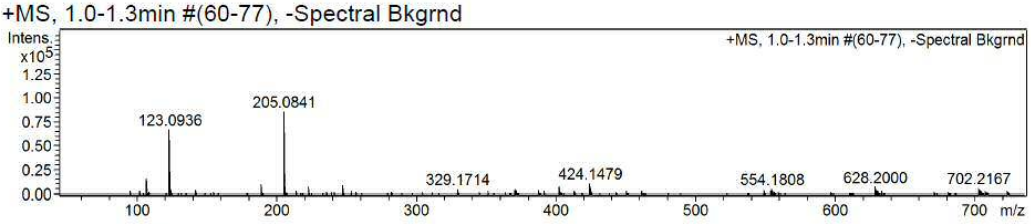
((3a*R*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methanol II-49



Confirmation of Expected Formula

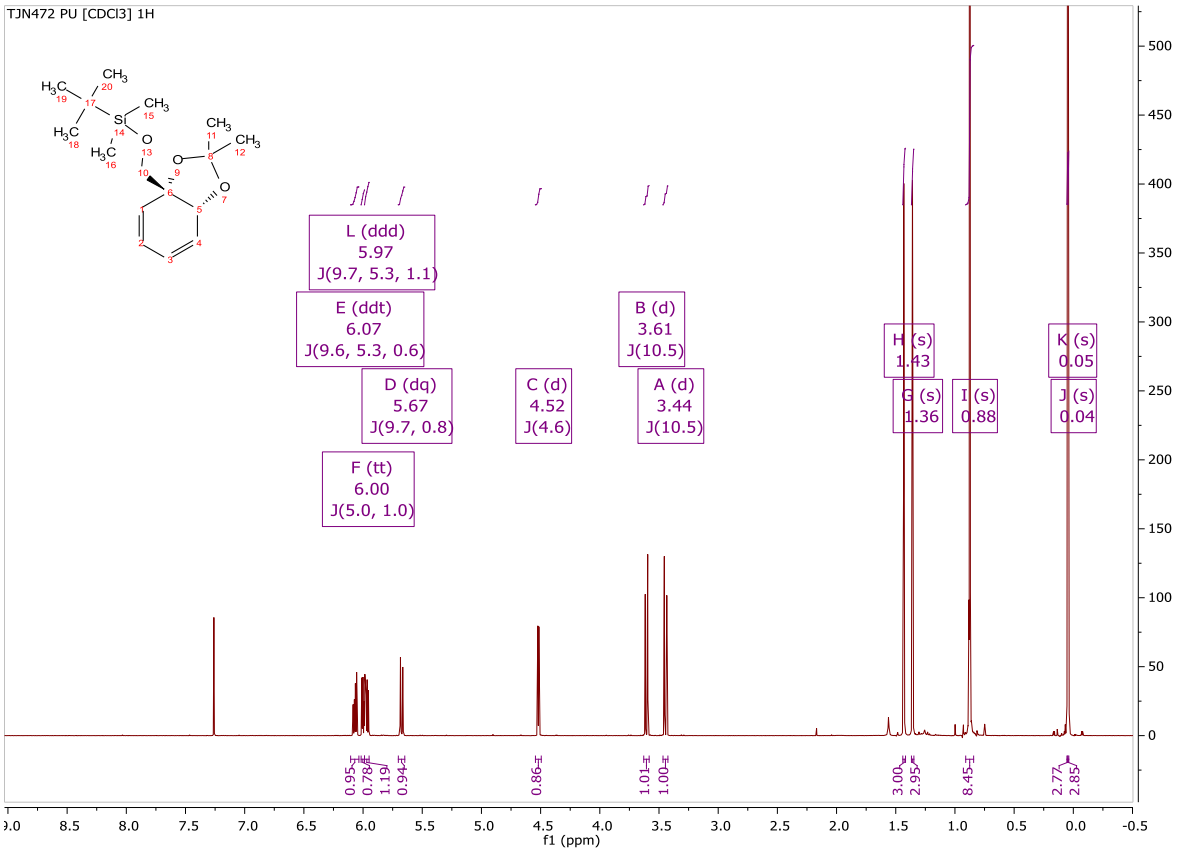
Sample-ID	tn_sel_065	Submitter	Toby Nash
Analysis Name	tn_sel_065_343960_17_01_48381.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	04/06/2015 14:57:32
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

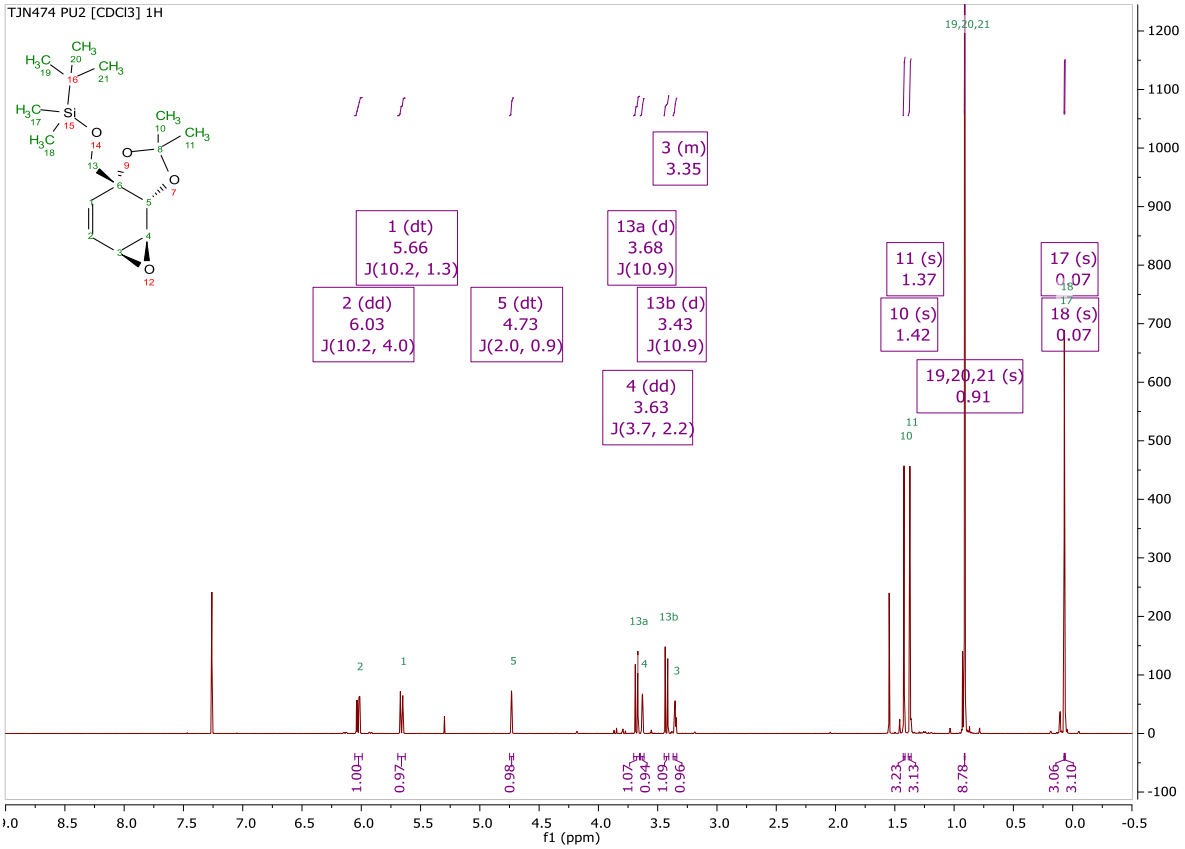


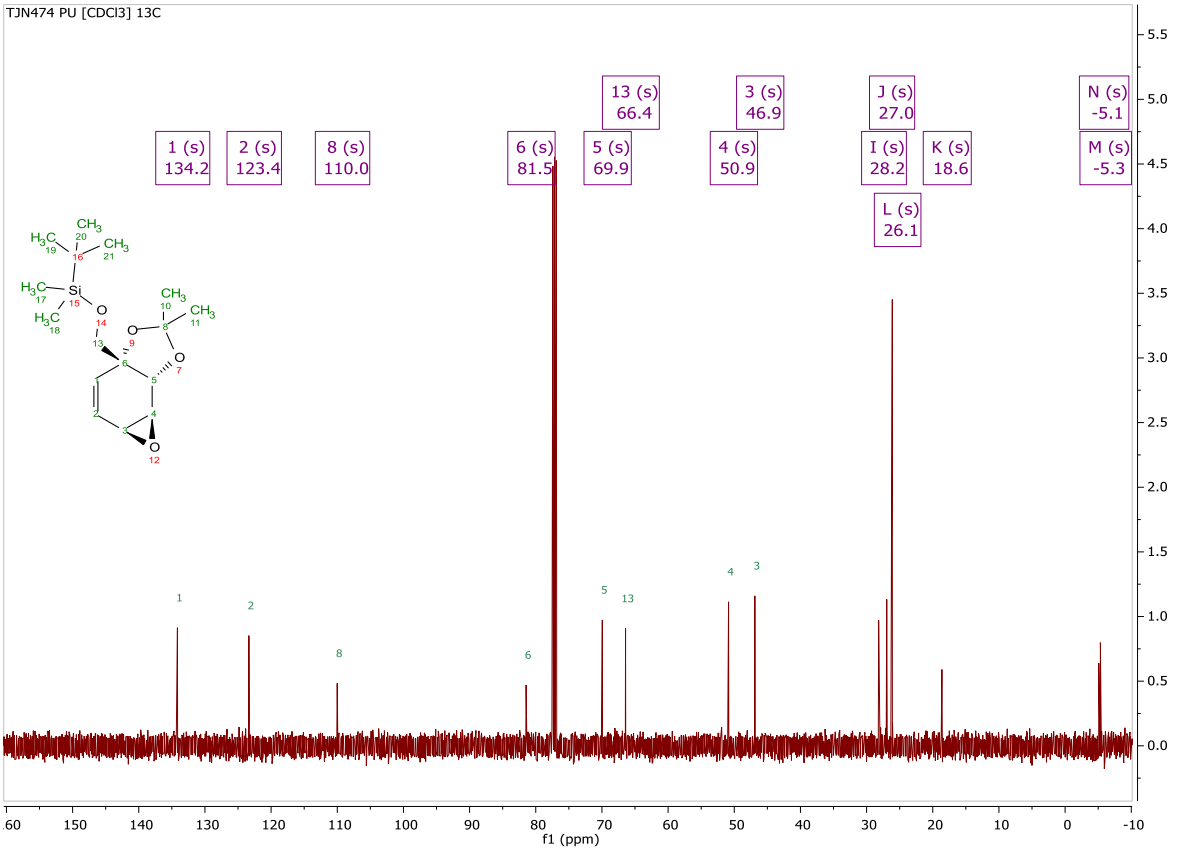
#	m/z	I	I %	Area	S/N
1	107.0498	15699	18.4	257	2192.1
2	123.0936	67057	78.5	1572	8706.1
3	189.1096	10206	12.0	431	779.7
4	205.0841	85377	100.0	3405	4897.7
5	206.0873	9825	11.5	410	556.6
6	223.0926	8246	9.7	435	489.4
7	247.0933	9325	10.9	461	593.4
8	402.1694	8384	9.8	794	256.0
9	424.1479	11585	13.6	1012	315.1
10	628.2000	7624	8.9	1224	88.3

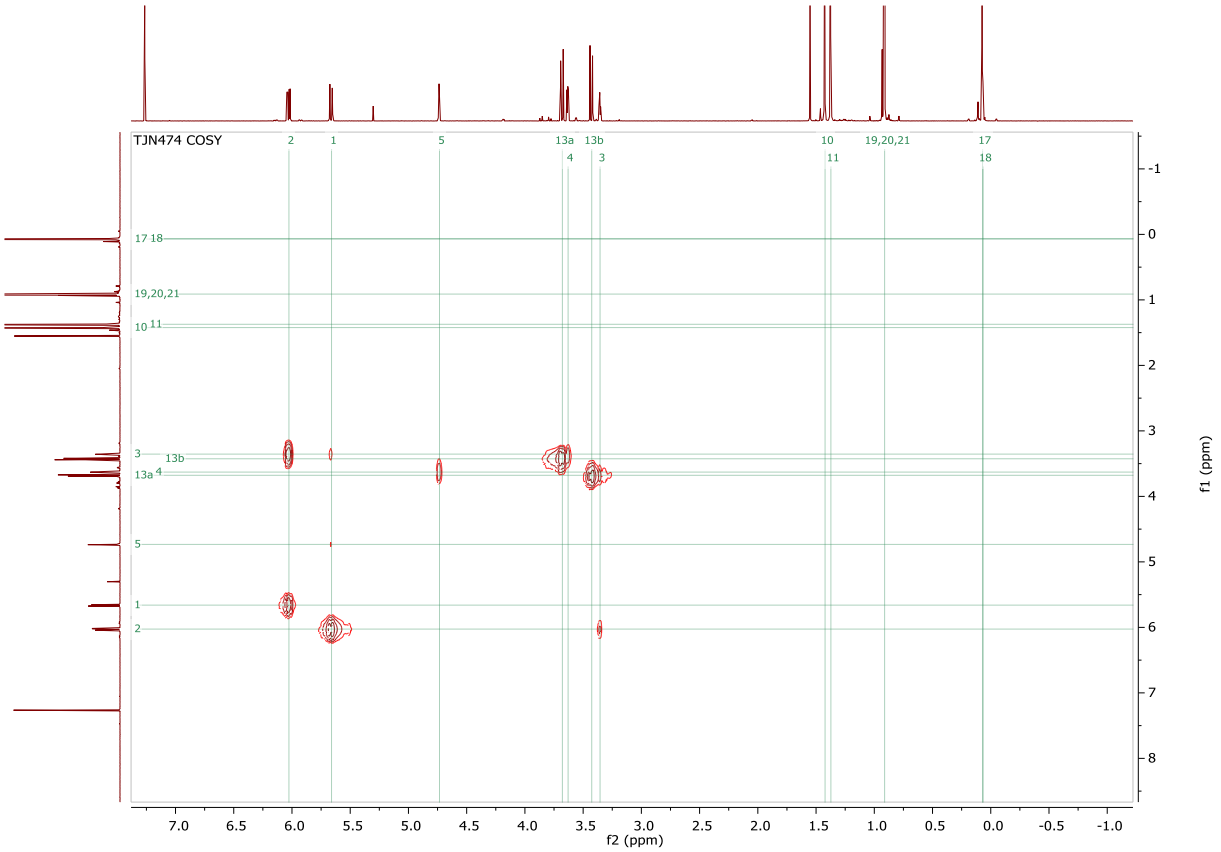
tert-Butyl(((3a_R_,7a_R_)-2,2-dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methoxy)dimethylsilane II-33

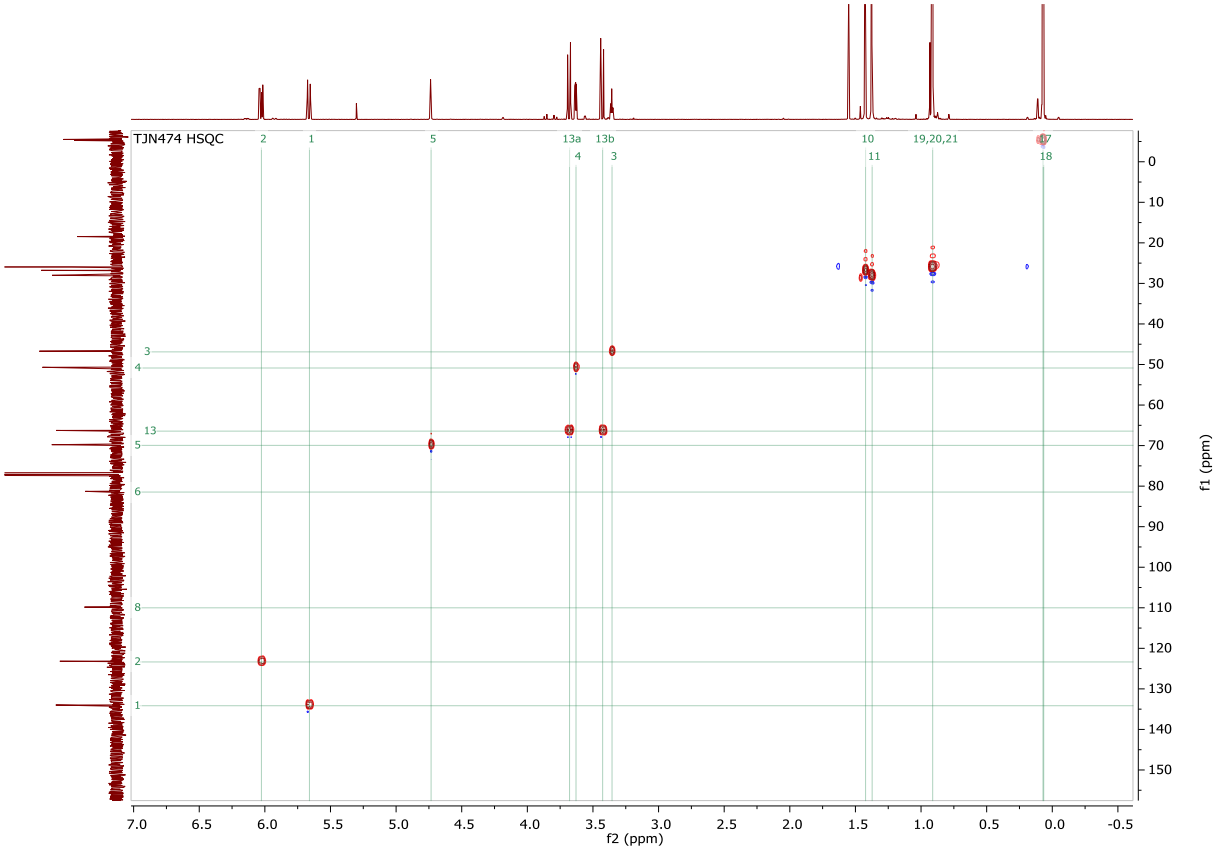


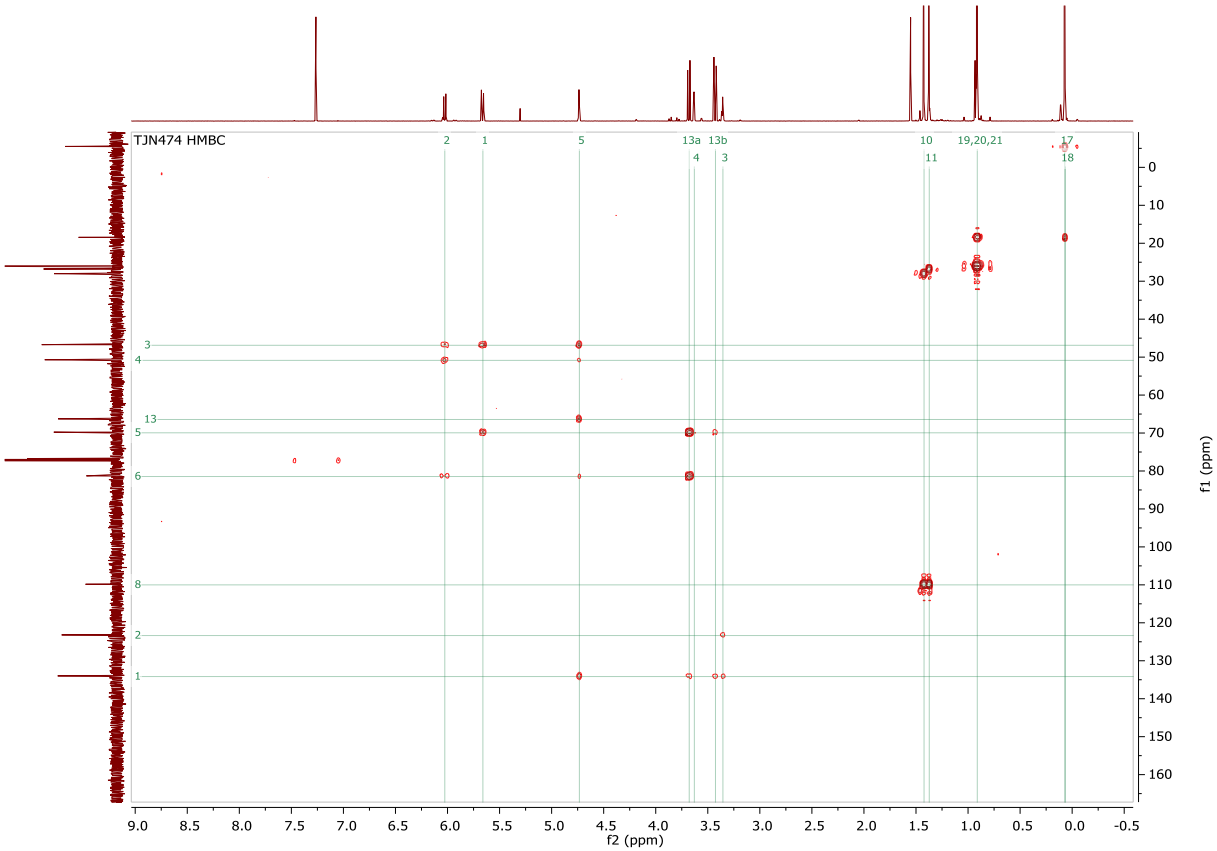
tert-Butyl(((3a*R*,5a*S*,6a*S*,6b*R*)-2,2-dimethyl-6a,6b-dihydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxol-3a(5aH)-yl)methoxy)dimethylsilane II-34






TJN474 COSY
f2 (ppm)
f1 (ppm)

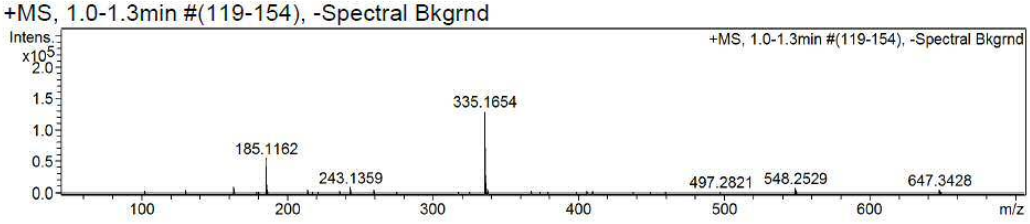

TJN474 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

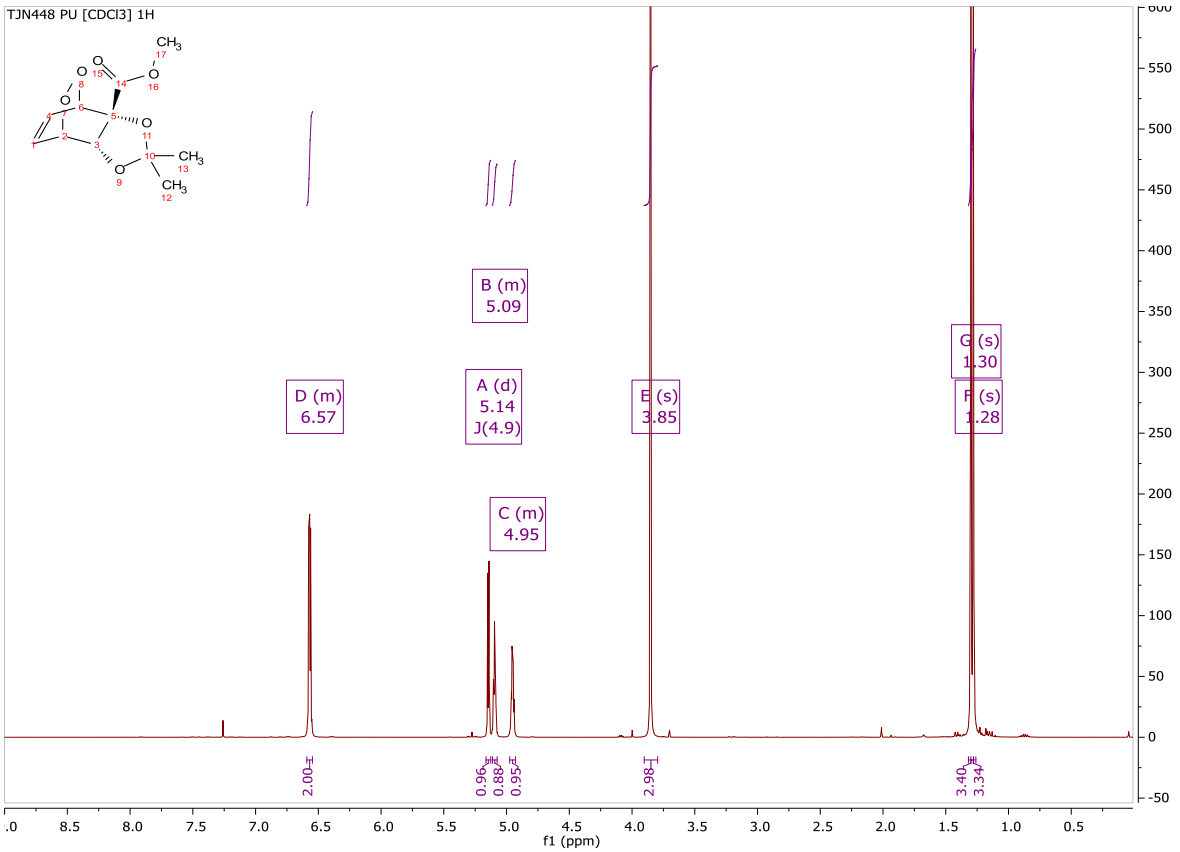
Sample-ID	tn_sel_TJN474	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN474_356341_34_01_62410.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	20/03/2018 16:21:16
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	163.0773	9634	7.4	273	2044.1
2	185.1162	55855	43.0	658	5005.6
3	186.1211	7768	6.0	92	678.3
4	243.1359	9312	7.2	402	823.2
5	259.1761	5612	4.3	65	531.3
6	335.1654	129925	100.0	7958	4240.0
7	336.1691	29504	22.7	1747	974.9
8	337.1652	6433	5.0	333	215.2
9	548.2529	8694	6.7	810	482.7
10	647.3428	5525	4.3	668	615.5

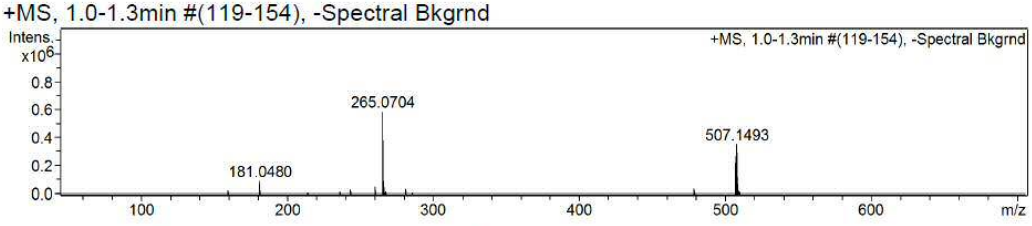
Methyl (3a*R*,4*R*,7*S*,7a*R*)-2,2-dimethyl-7,7a-dihydro-4,7-epidioxybenzo[d][1,3]dioxole-3a(4H)-carboxylate II-35



Confirmation of Expected Formula

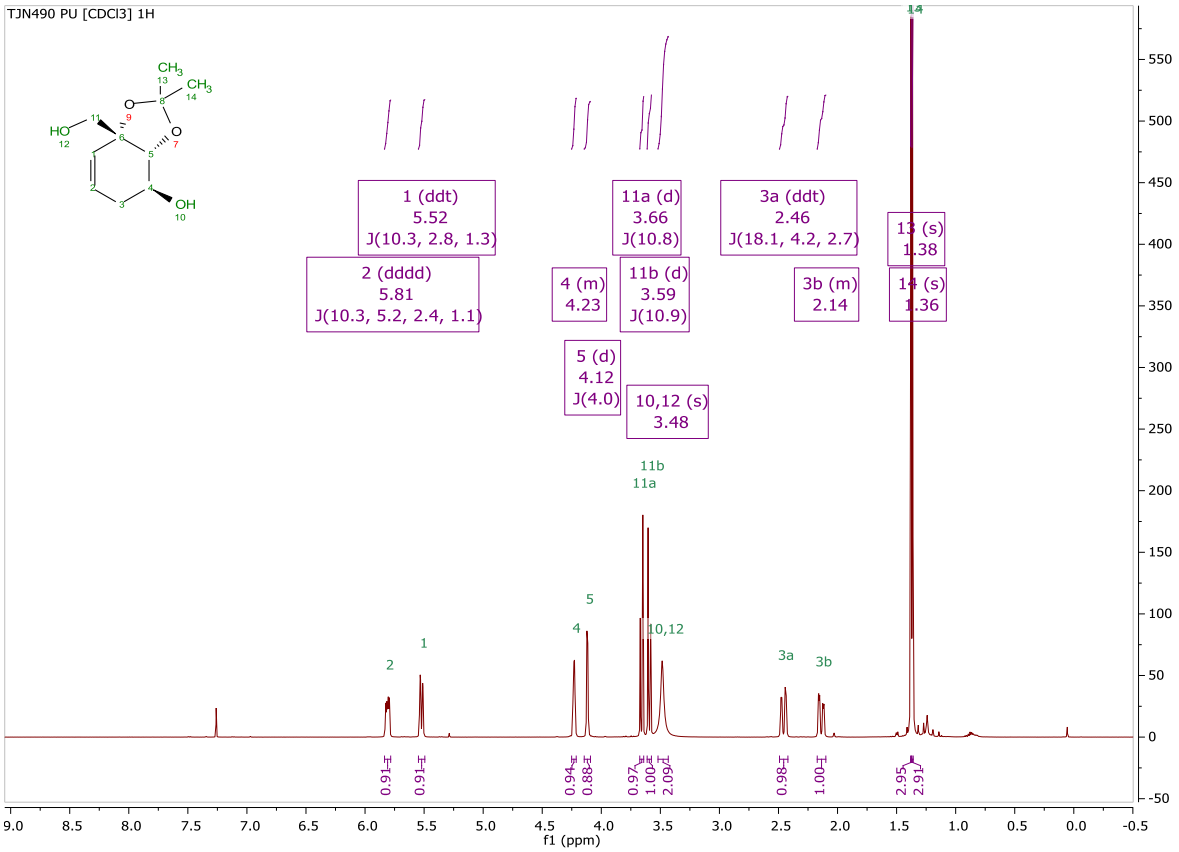
Sample-ID	tn_sel_TJN448	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN448_355364_38_01_61183.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	12/01/2018 10:50:12
Ionisation Mode	positive electrospray (ESI)		

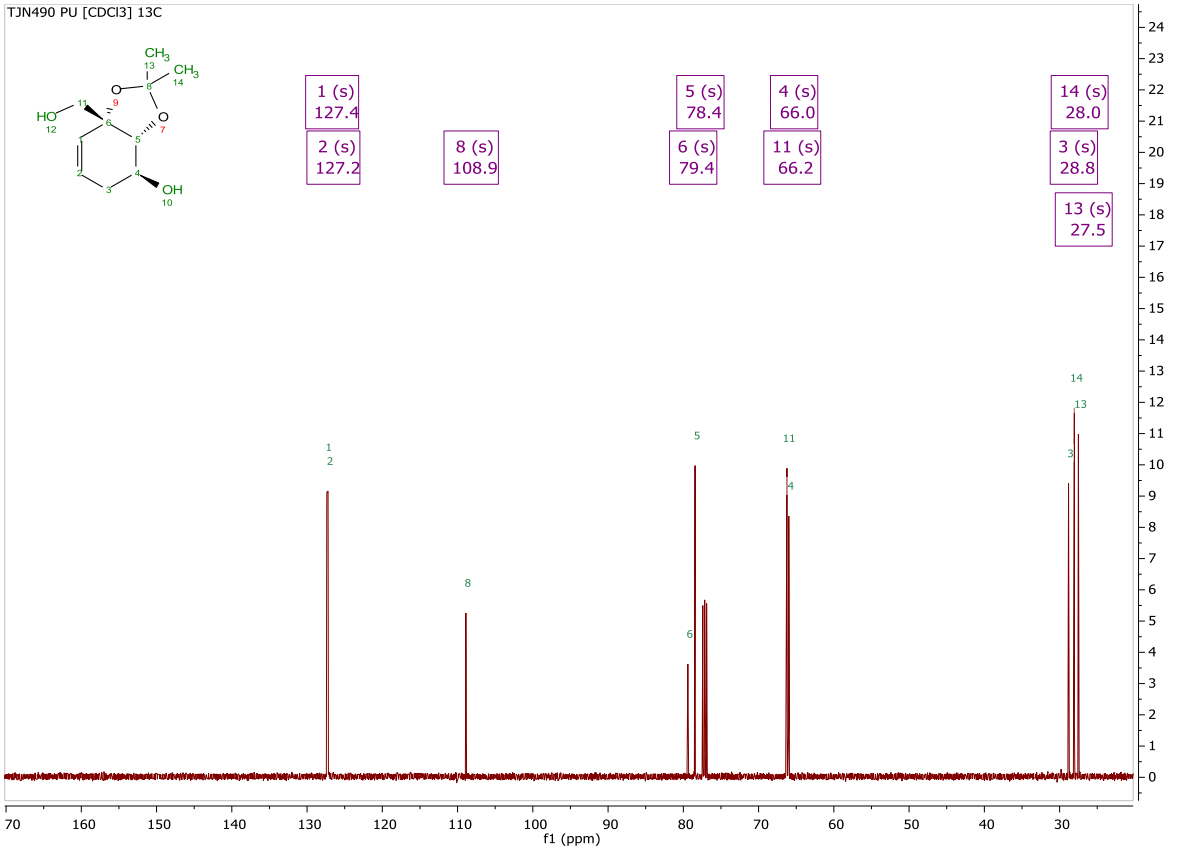
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

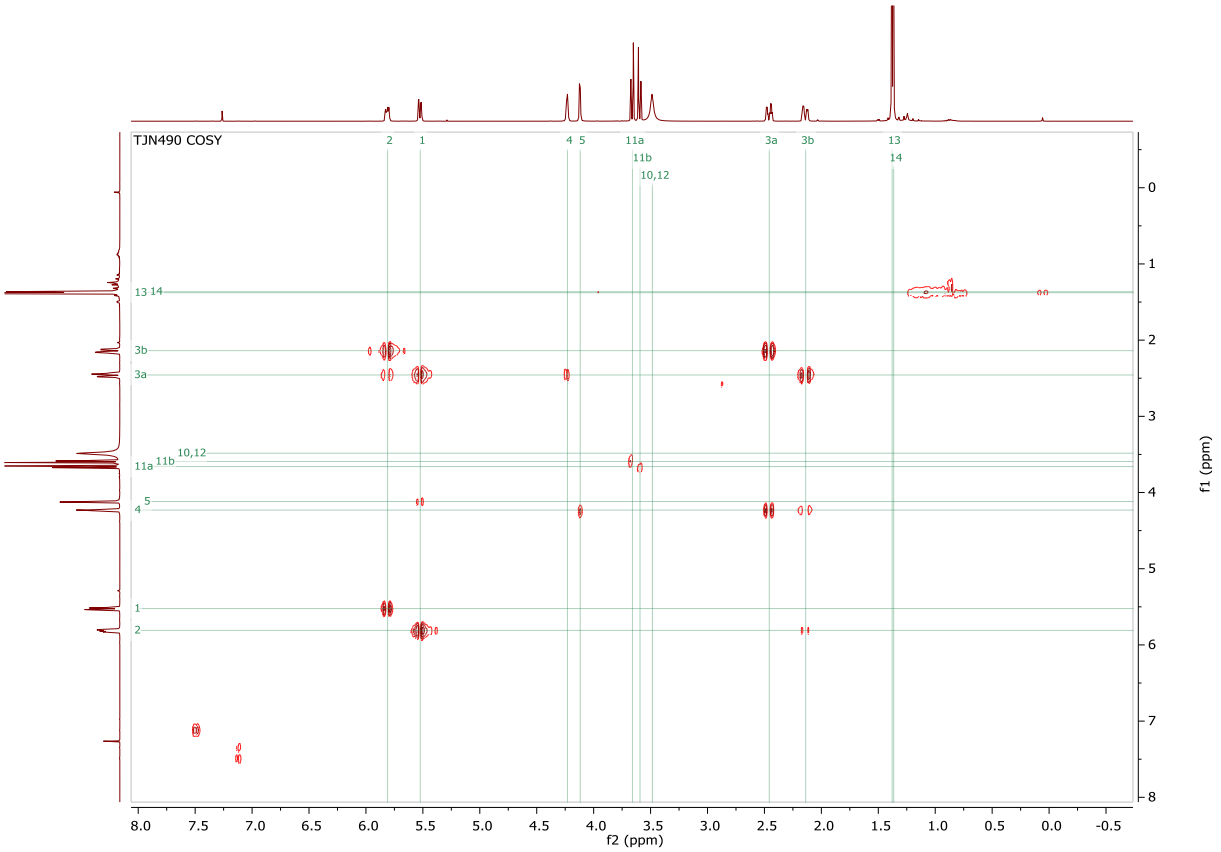


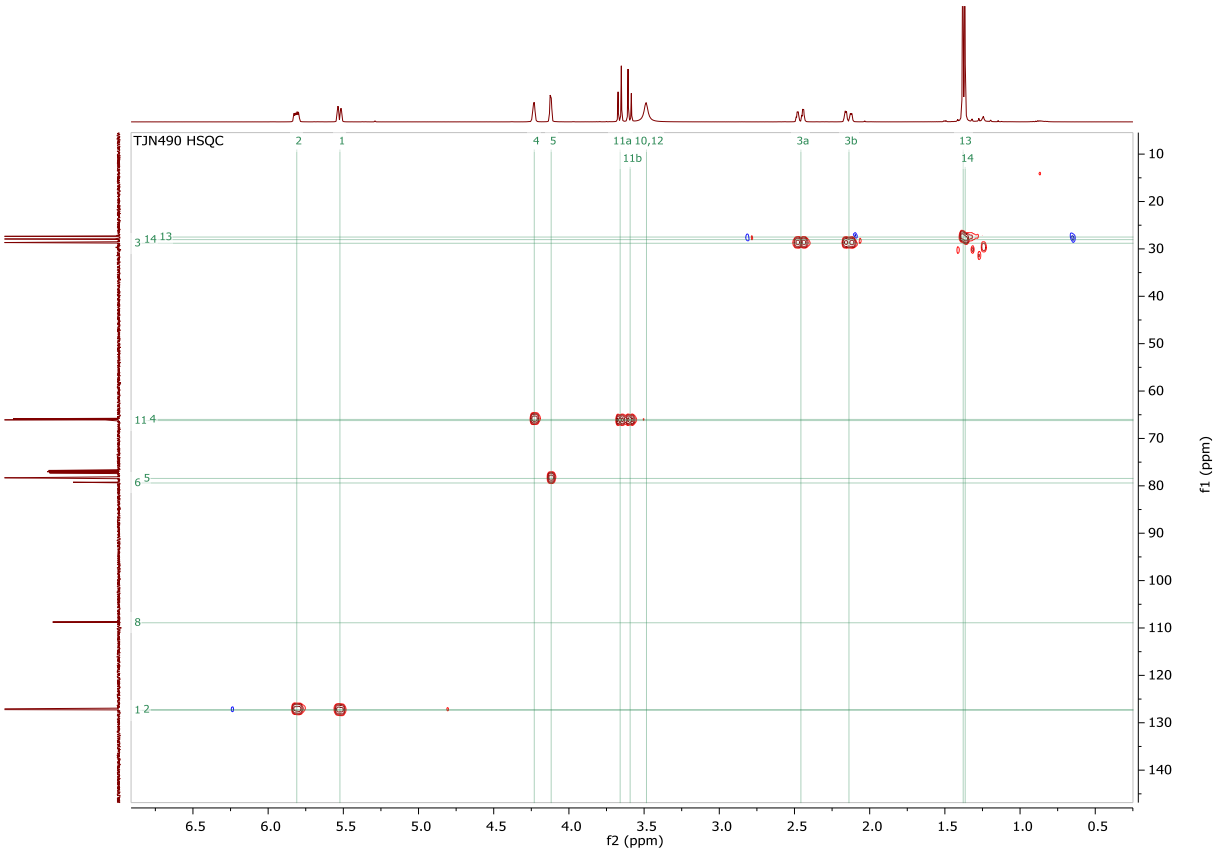
#	m/z	I	I %	Area	S/N
1	159.0668	22548	3.9	682	1918.6
2	181.0480	90706	15.5	3379	5021.2
3	243.0854	26812	4.6	1198	709.6
4	260.1136	51095	8.7	2455	1209.0
5	265.0704	584746	100.0	31206	13423.0
6	266.0722	74477	12.7	3765	1699.3
7	281.0425	36828	6.3	1908	771.0
8	478.1524	36702	6.3	2929	1169.7
9	507.1493	352317	60.3	34386	6735.1
10	508.1524	83897	14.3	7870	1635.2

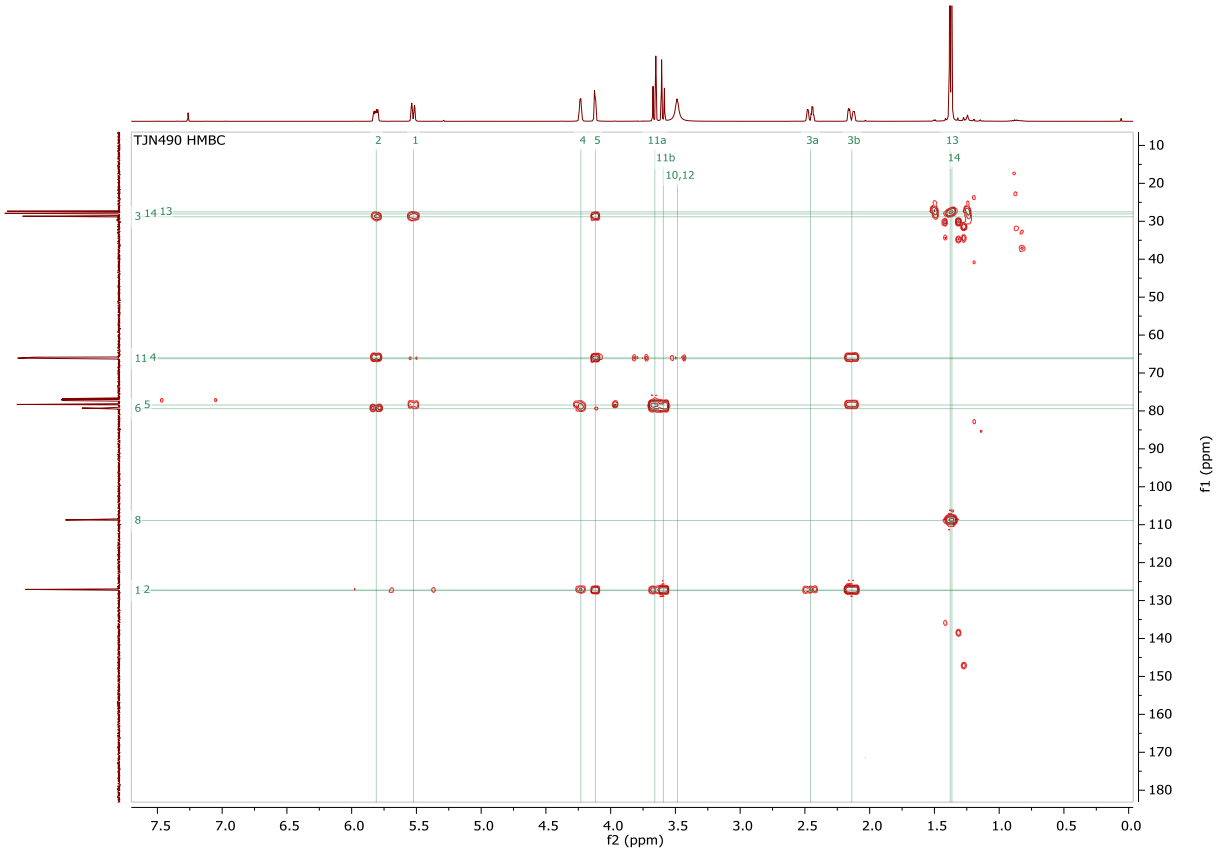
(3a*R*,4*S*,7a*R*)-7a-(Hydroxymethyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol II-36






TJN490 COSY
f2 (ppm)
f1 (ppm)

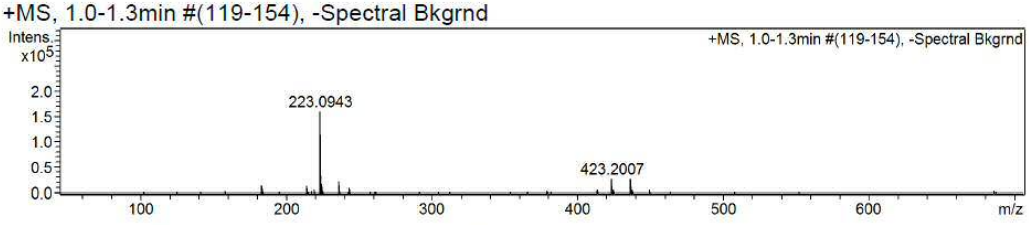

TJN490 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

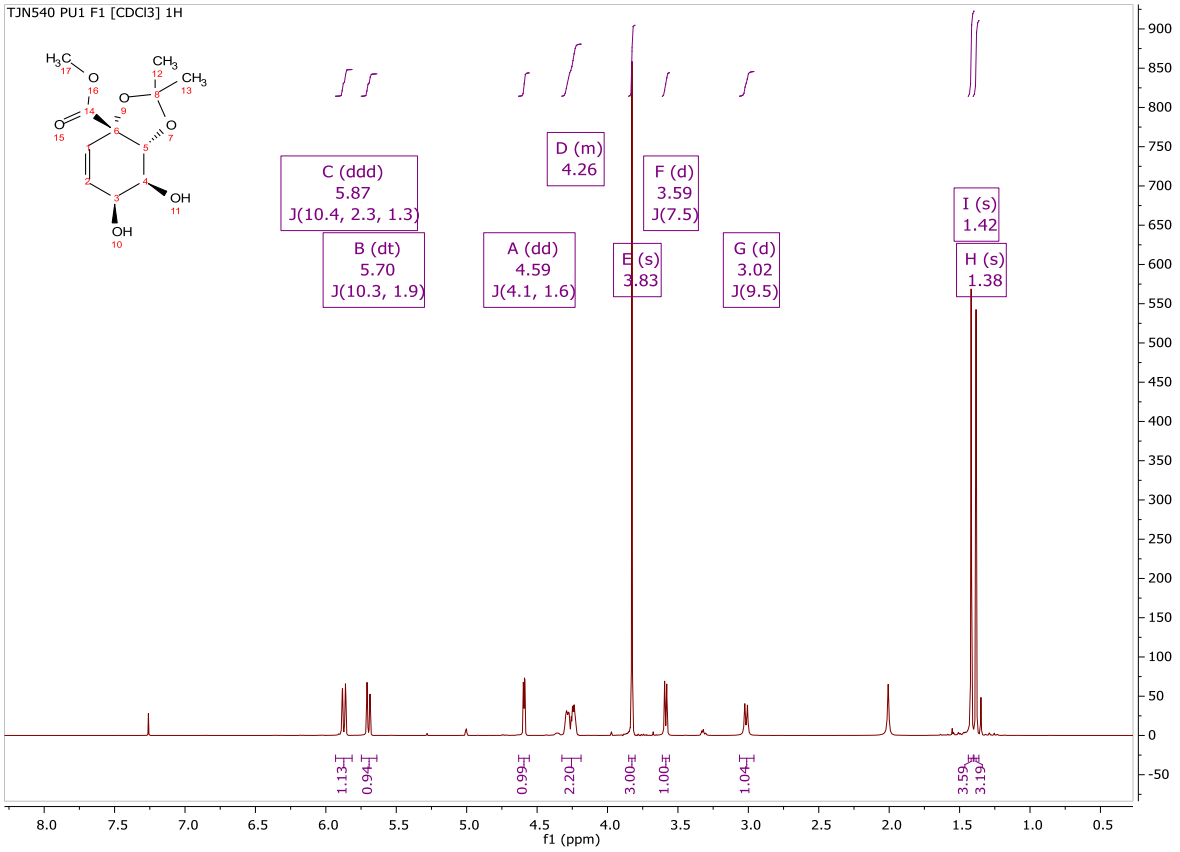
Sample-ID	tn_sel_TJN490	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN490 _356681_60_01_62779.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	11/04/2018 16:48:37
Ionisation Mode	positive electrospray (ESI)		

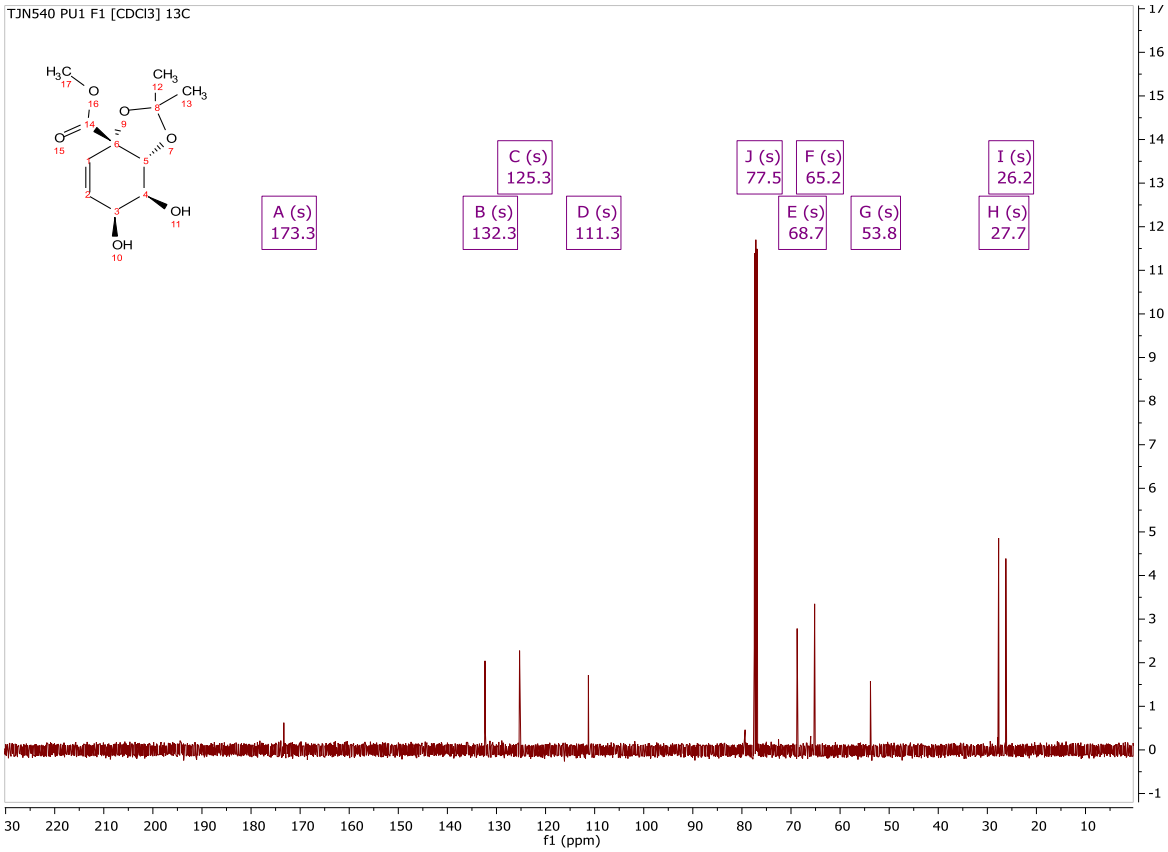
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd



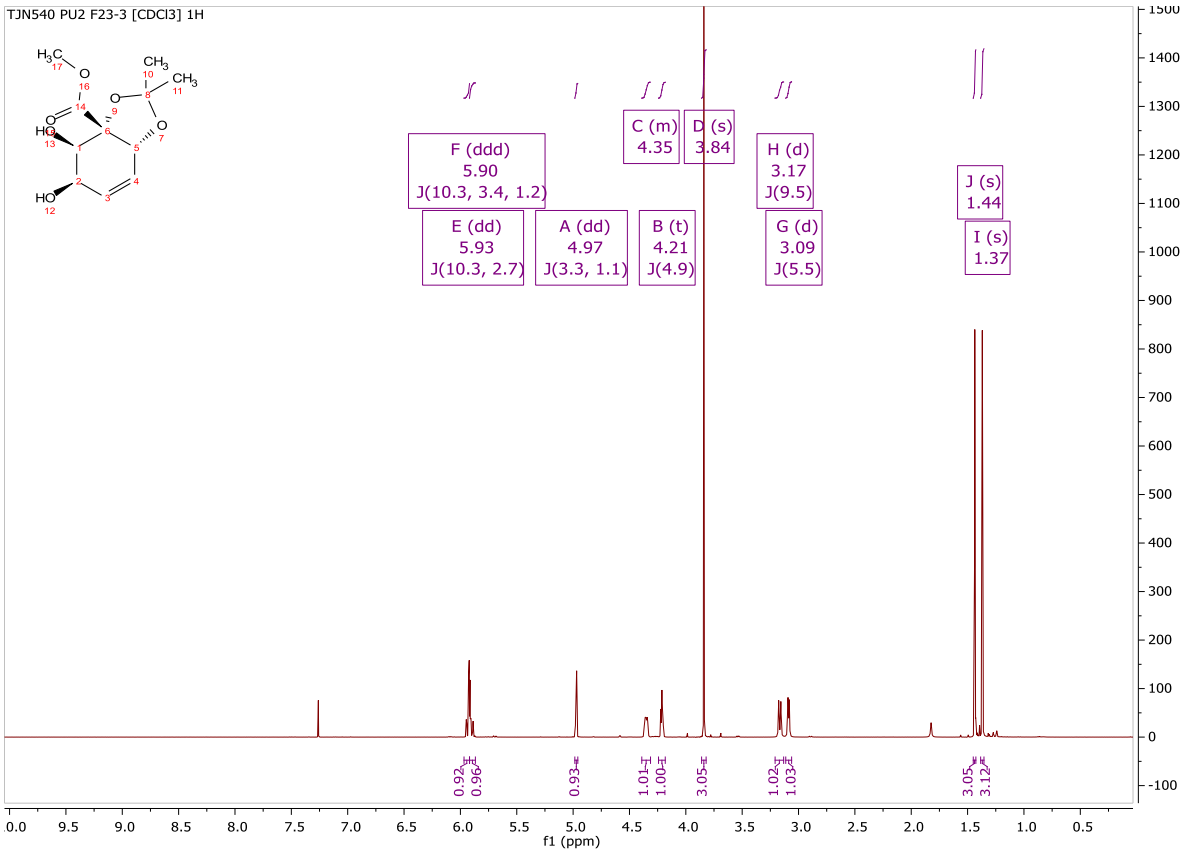
#	m/z	I	I %	Area	S/N
1	183.0634	14620	9.1	431	1890.2
2	214.0940	12828	8.0	341	564.3
3	223.0943	160941	100.0	7432	5391.9
4	224.0973	17511	10.9	725	571.5
5	236.0855	23657	14.7	337	589.6
6	243.1374	10714	6.7	461	235.1
7	423.2007	29295	18.2	2253	858.1
8	436.1786	28731	17.9	2198	948.1
9	437.1773	6650	4.1	458	221.6
10	449.1737	7050	4.4	291	266.4

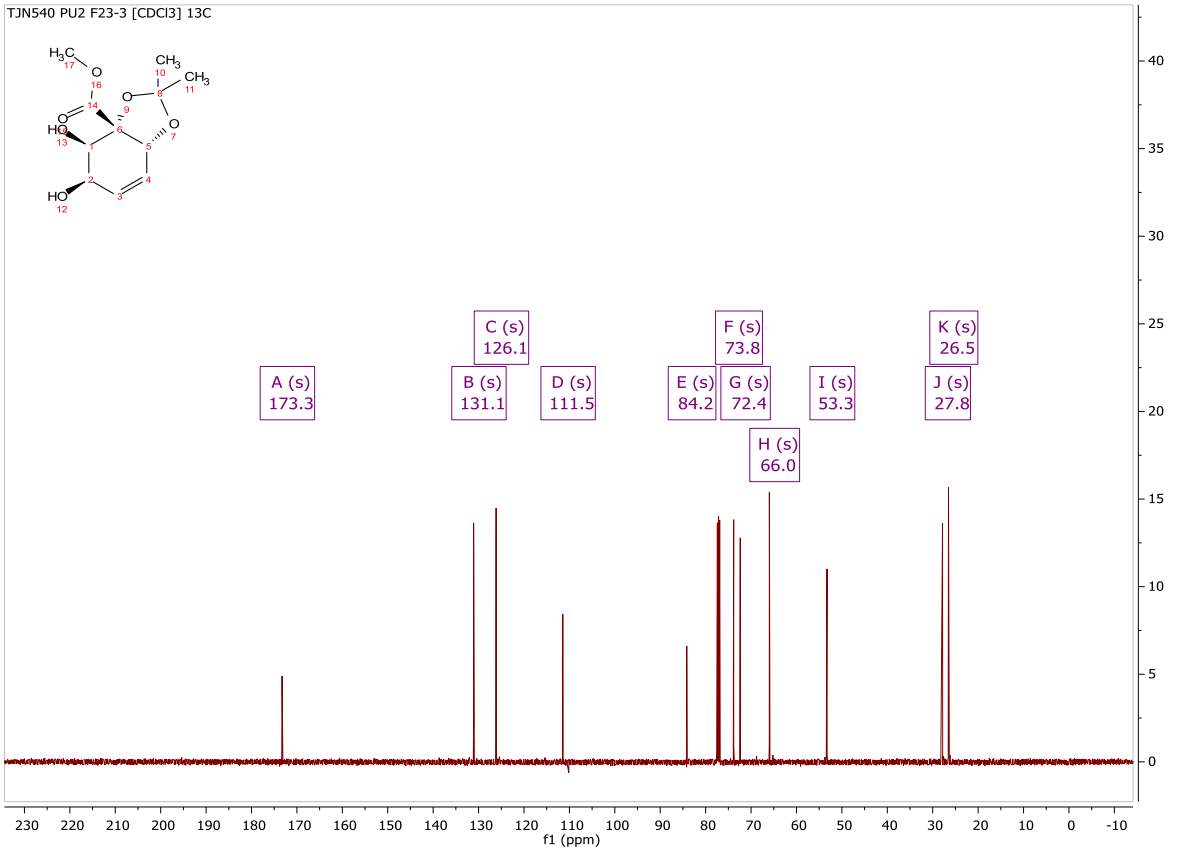
Methyl (3a*S*,6*S*,7*S*,7a*R*)-6,7-dihydroxy-2,2-dimethyl-7,7a-dihydrobenzo[d][1,3]dioxole-3a(6H)-carboxylate II-40



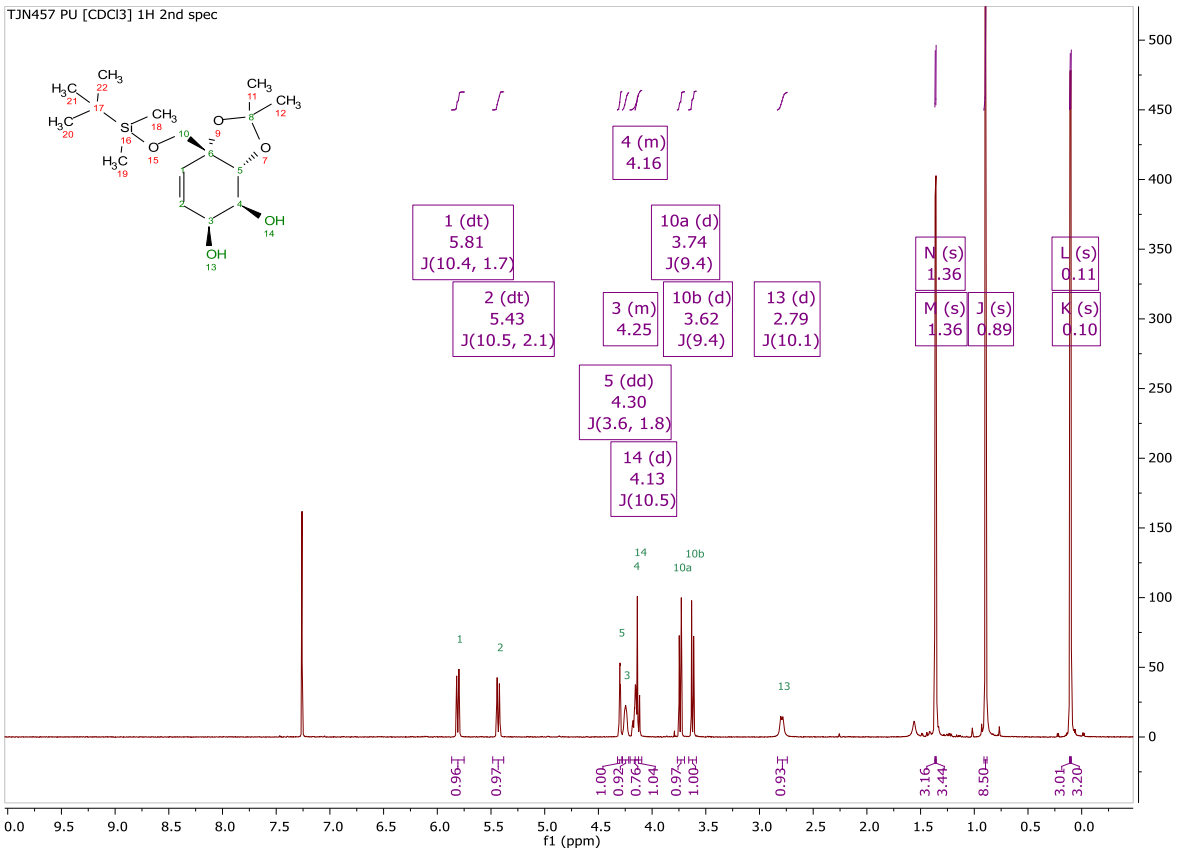

TJN540 PU1 F1 [CDCl3] 13C
A (s)
173.3
B (s)
132.3
C (s)
125.3
D (s)
111.3
E (s)
68.7
F (s)
65.2
G (s)
53.8
H (s)
27.7
I (s)
26.2
J (s)
77.5
f1 (ppm)

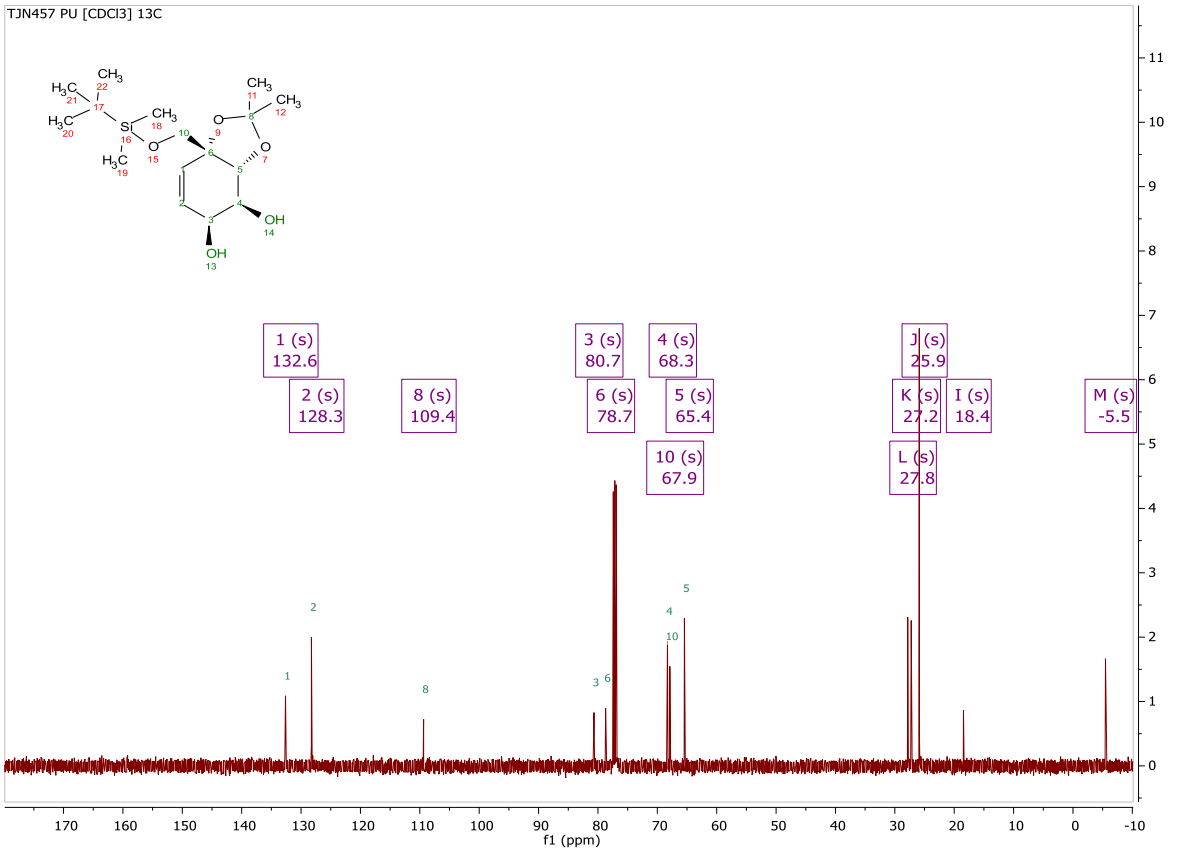
Methyl (3a*S*,4*R*,5*R*,7a*R*)-4,5-dihydroxy-2,2-dimethyl-5,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate II-42

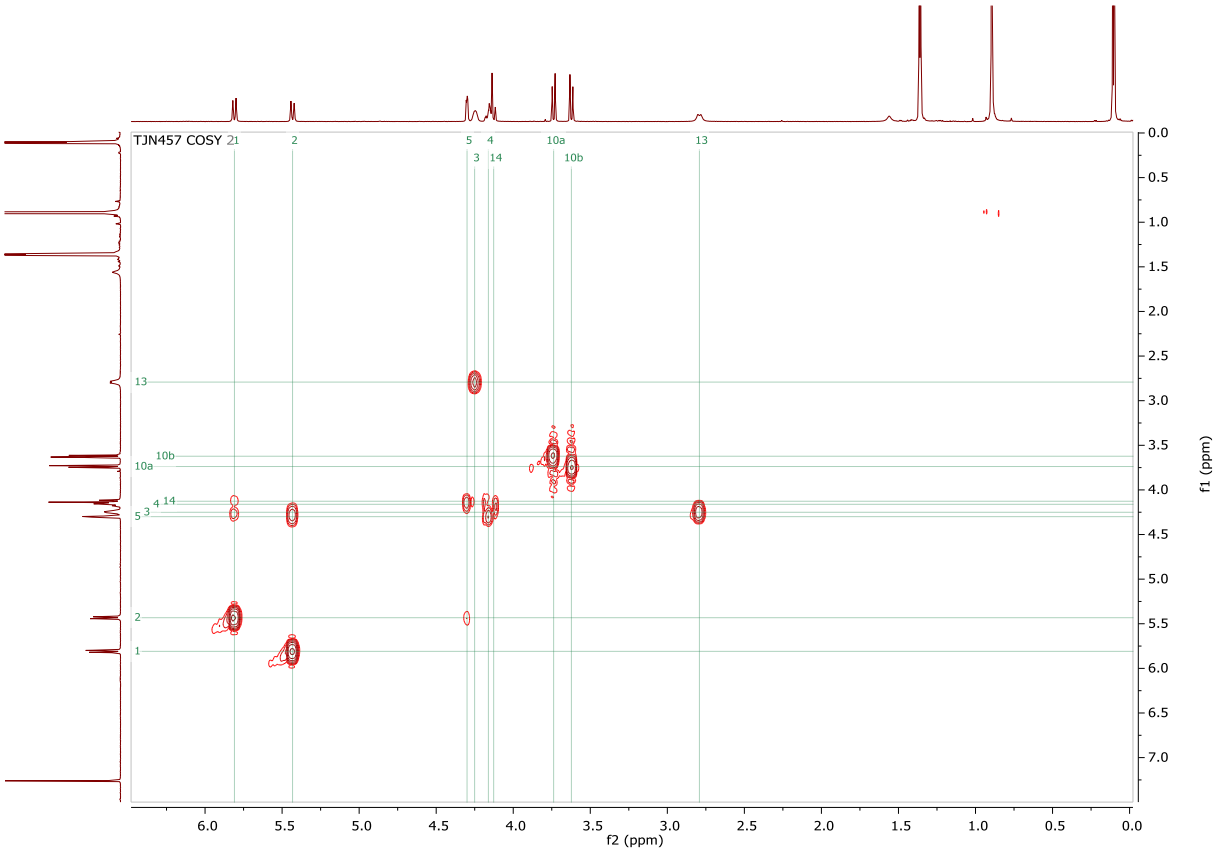


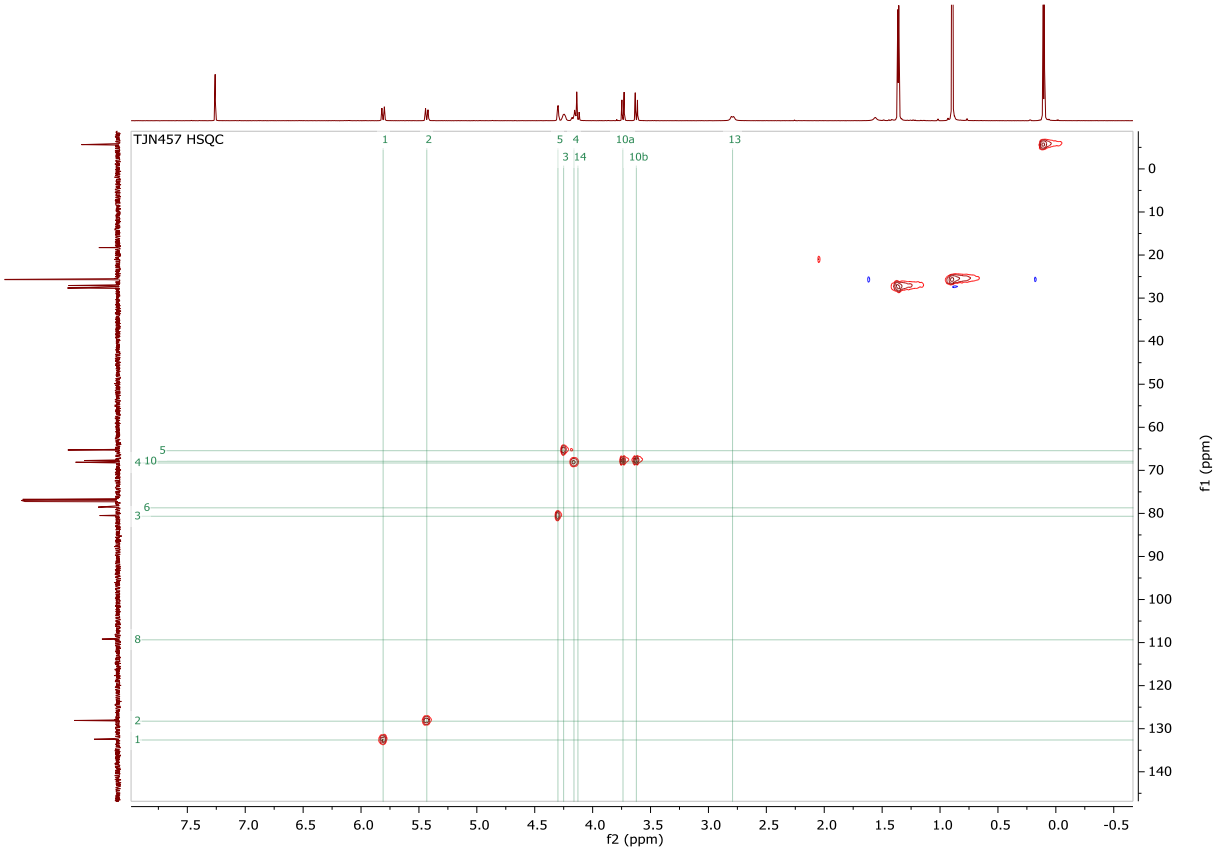


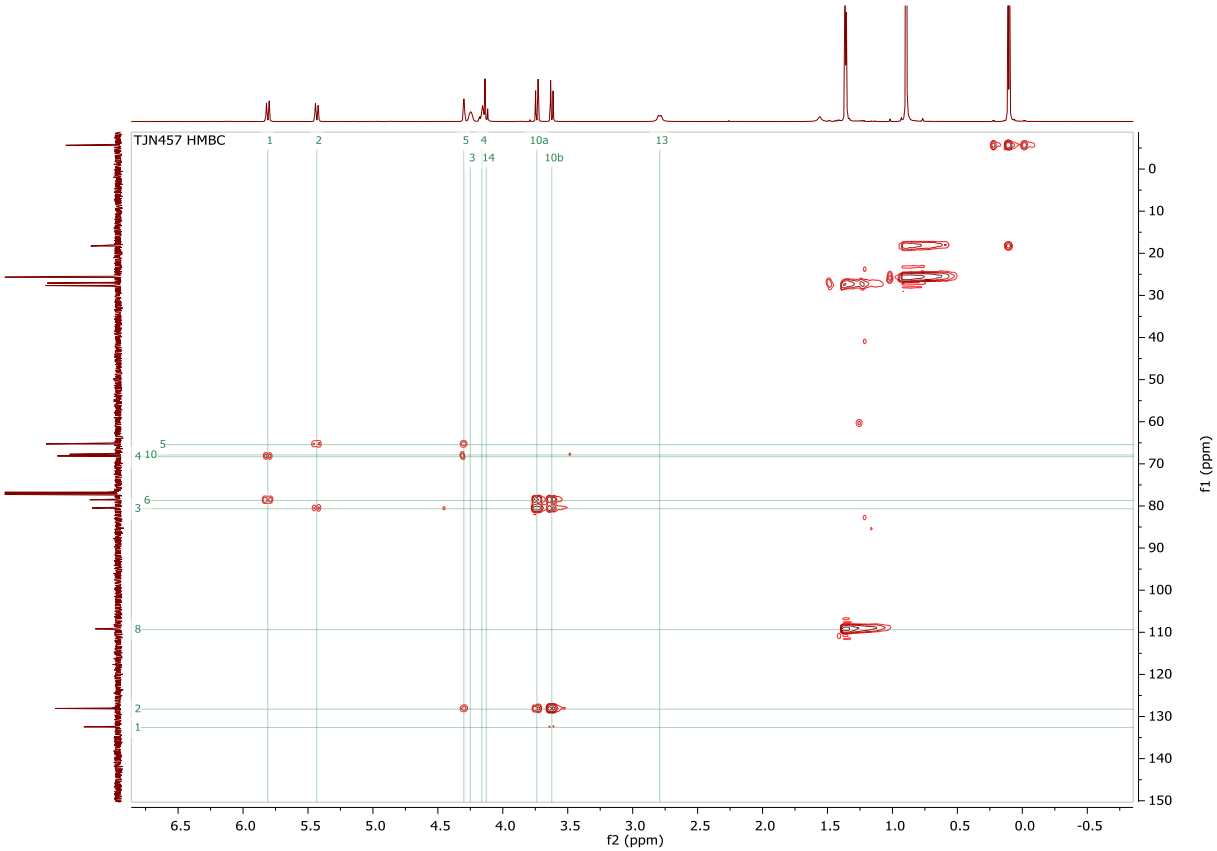
(3a*R*,4*S*,5*S*,7a*R*)-7a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxole-4,5-diol II-43






TJN457 COSY
f2 (ppm)
f1 (ppm)

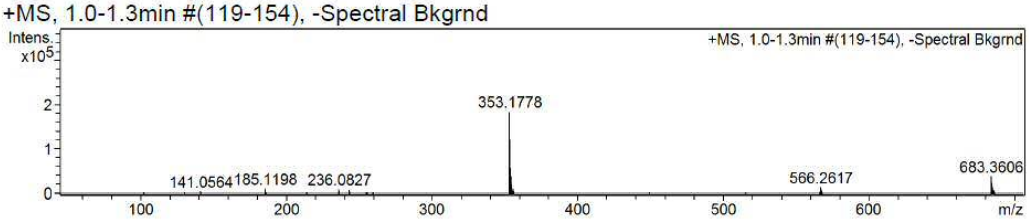

TJN457 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

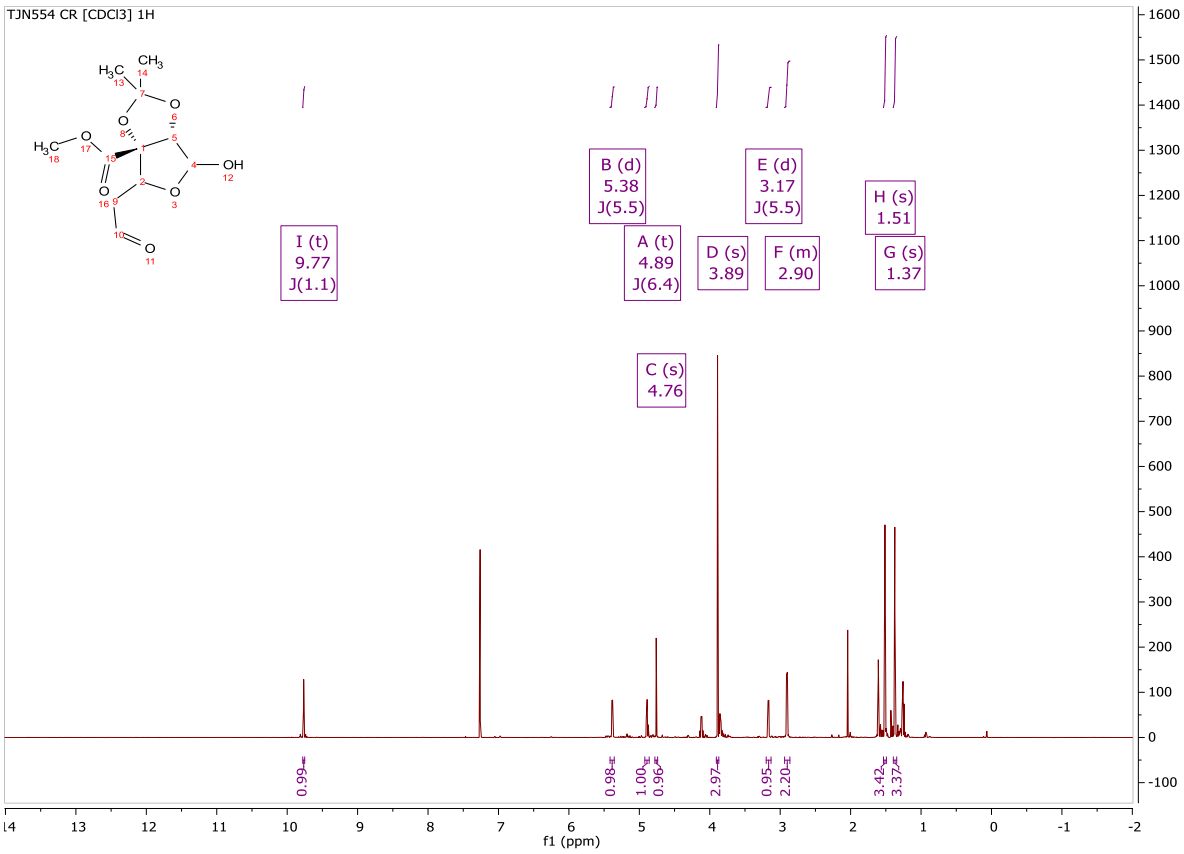
Sample-ID	tn_sel_TJN457	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN457_356342_35_01_62411.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	20/03/2018 16:24:46
Ionisation Mode	positive electrospray (ESI)		

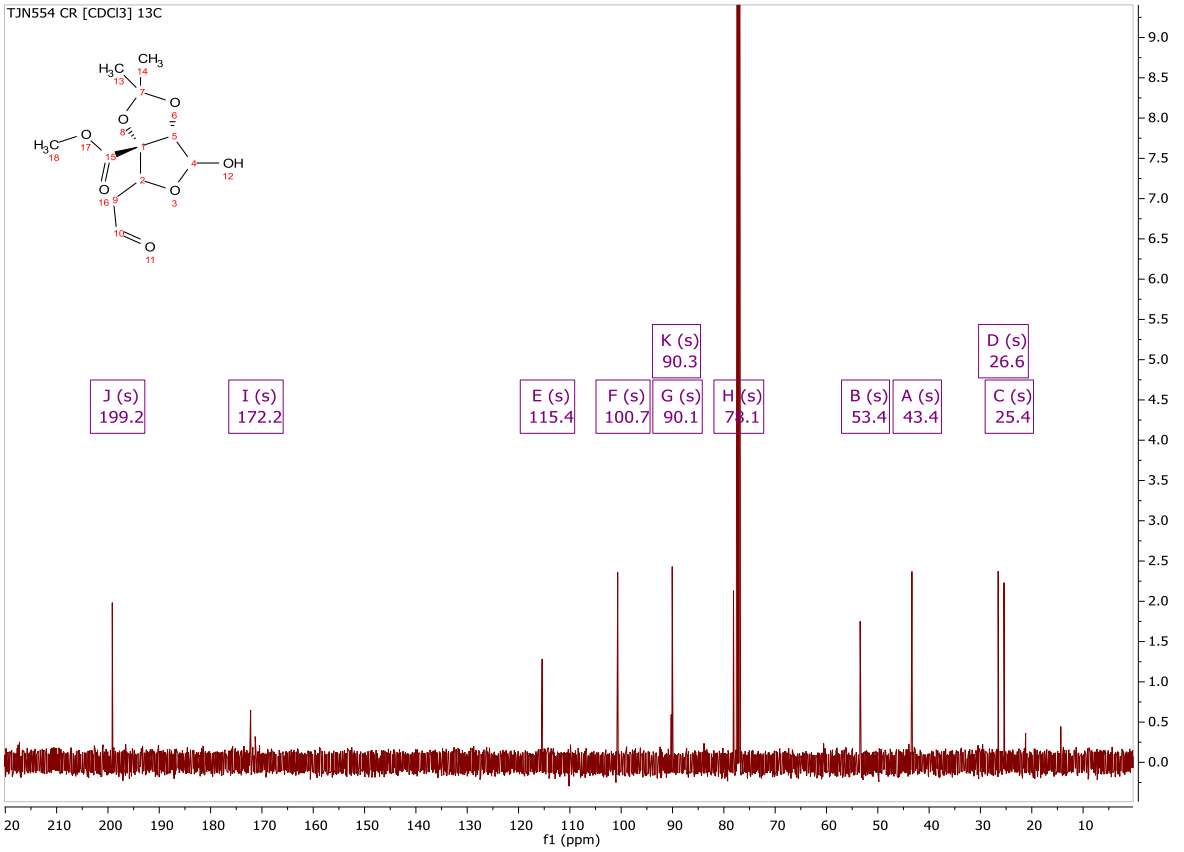
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	185.1198	10443	5.7	192	2046.5
2	236.0827	9654	5.2	112	1055.6
3	243.1355	6682	3.6	263	696.8
4	353.1778	184498	100.0	12292	8703.9
5	354.1808	39856	21.6	2354	1841.0
6	355.1788	10581	5.7	662	478.8
7	566.2617	13783	7.5	1327	1028.7
8	683.3606	38118	20.7	4924	2092.9
9	684.3629	16911	9.2	2368	928.4
10	685.3627	6773	3.7	929	371.7

Methyl (3a*S*,6a*S*)-6-hydroxy-2,2-dimethyl-4-(2-oxoethyl)dihydrofuro[3,4-d][1,3]dioxole-3a(4H)-carboxylate II-39

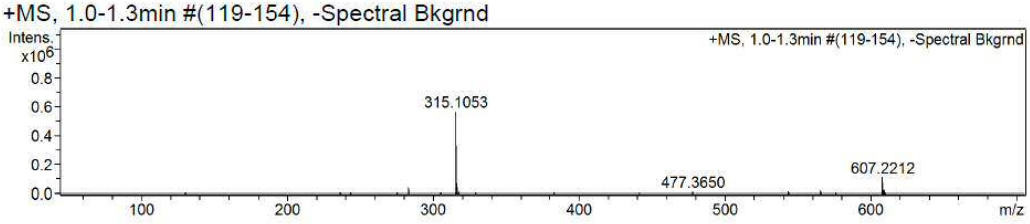




Confirmation of Expected Formula

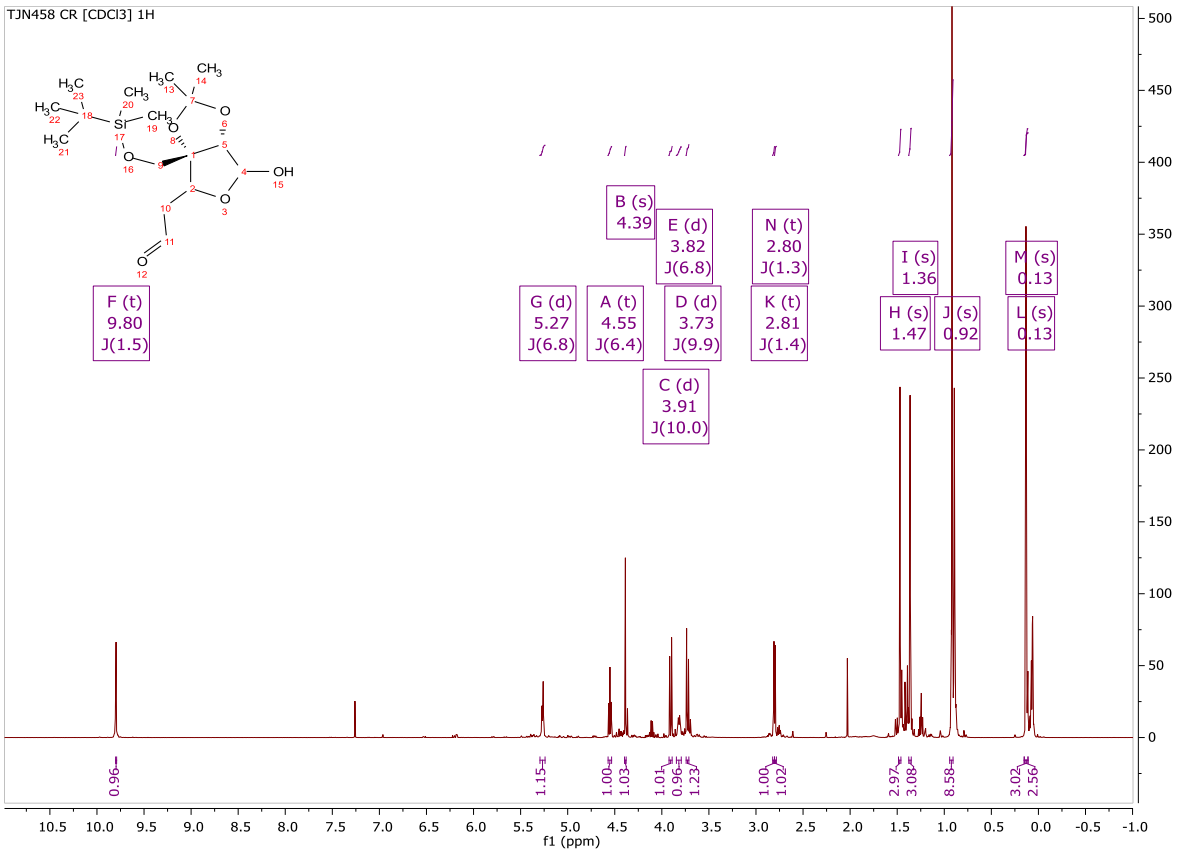
Sample-ID	tn_sel_TJN554	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN554_358850_55_01_65271.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	18/09/2018 11:53:40
Ionisation Mode	positive electrospray (ESI)		

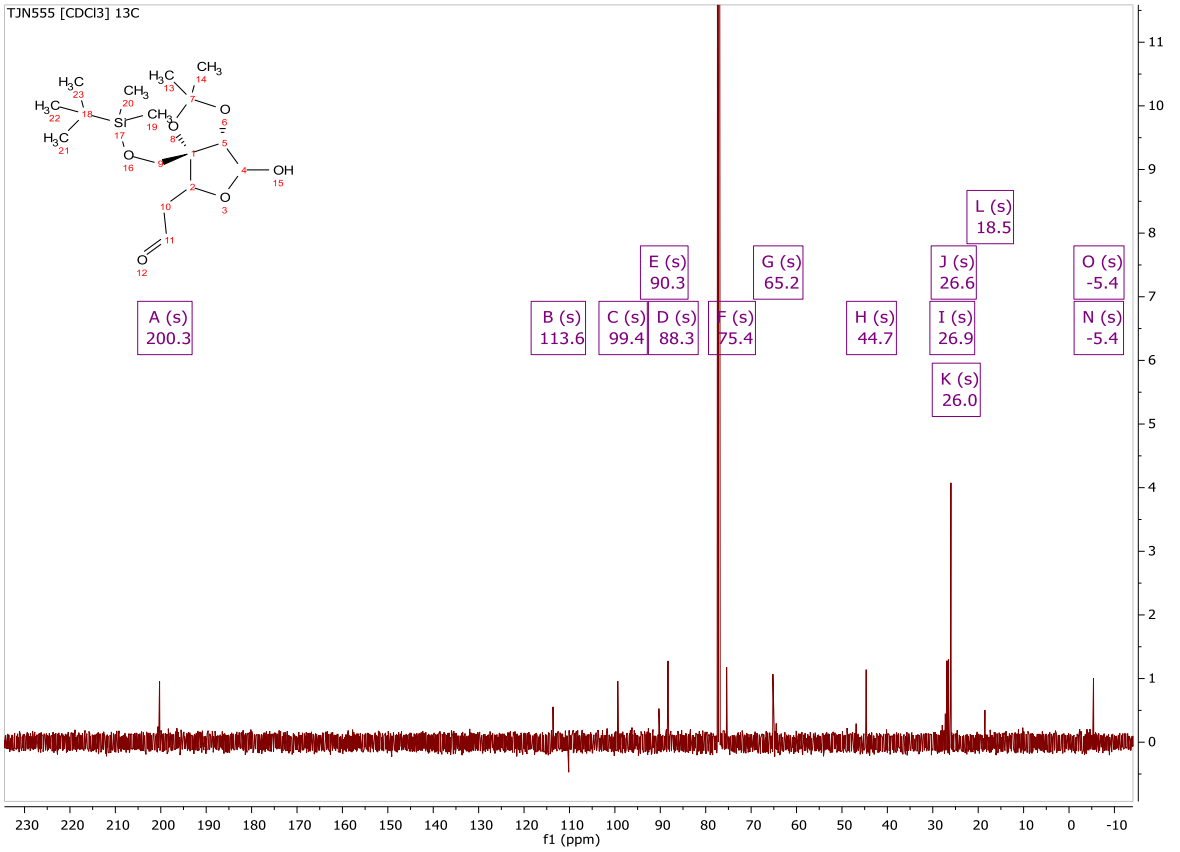
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	283.0792	41626	7.4	1835	1188.1
2	305.0604	10809	1.9	568	206.1
3	315.1053	564331	100.0	35082	9243.8
4	316.1084	72108	12.8	4156	1164.4
5	317.1099	12660	2.2	680	201.5
6	477.3650	14073	2.5	1196	745.7
7	543.1686	13110	2.3	1304	520.4
8	565.1504	20901	3.7	2206	605.5
9	607.2212	112919	20.0	13533	2959.8
10	608.2240	28983	5.1	3471	776.9

2-((3a*S*,6a*S*)-3a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-hydroxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)acetaldehyde II-44

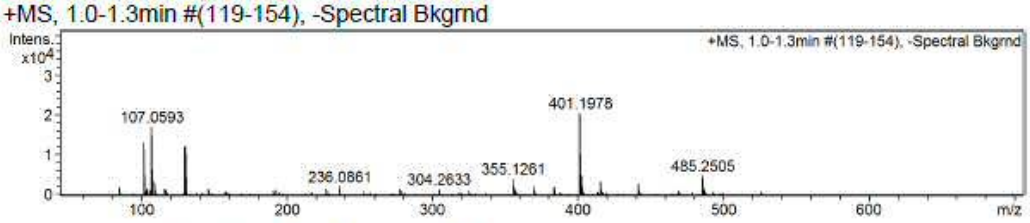




Confirmation of Expected Formula

Sample-ID	tn_sel_TJN555	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN555_358886_90_01_65317.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	20/09/2018 16:43:39
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	102.1300	13074	63.9	236	4304.3
2	107.0593	17067	83.4	112	4948.6
3	109.0497	3312	16.2	24	916.2
4	130.1618	12335	60.2	331	4392.3
5	355.1261	4152	20.3	213	611.3
6	401.1978	20476	100.0	1479	1923.0
7	402.2008	4912	24.0	341	457.7
8	415.2161	3369	16.5	247	285.7
9	441.3222	2827	13.8	65	292.0
10	485.2505	4814	23.5	411	619.4

Generate Molecular Formula Parameters

Charge	Tolerance	SearchRadius	H/C Ratio min.	H/C Ratio max.	Electron Conf.	Nitrogen Rule	sigma limit
positive	25 ppm	0.05 m/z	0	3	both	true	0.05

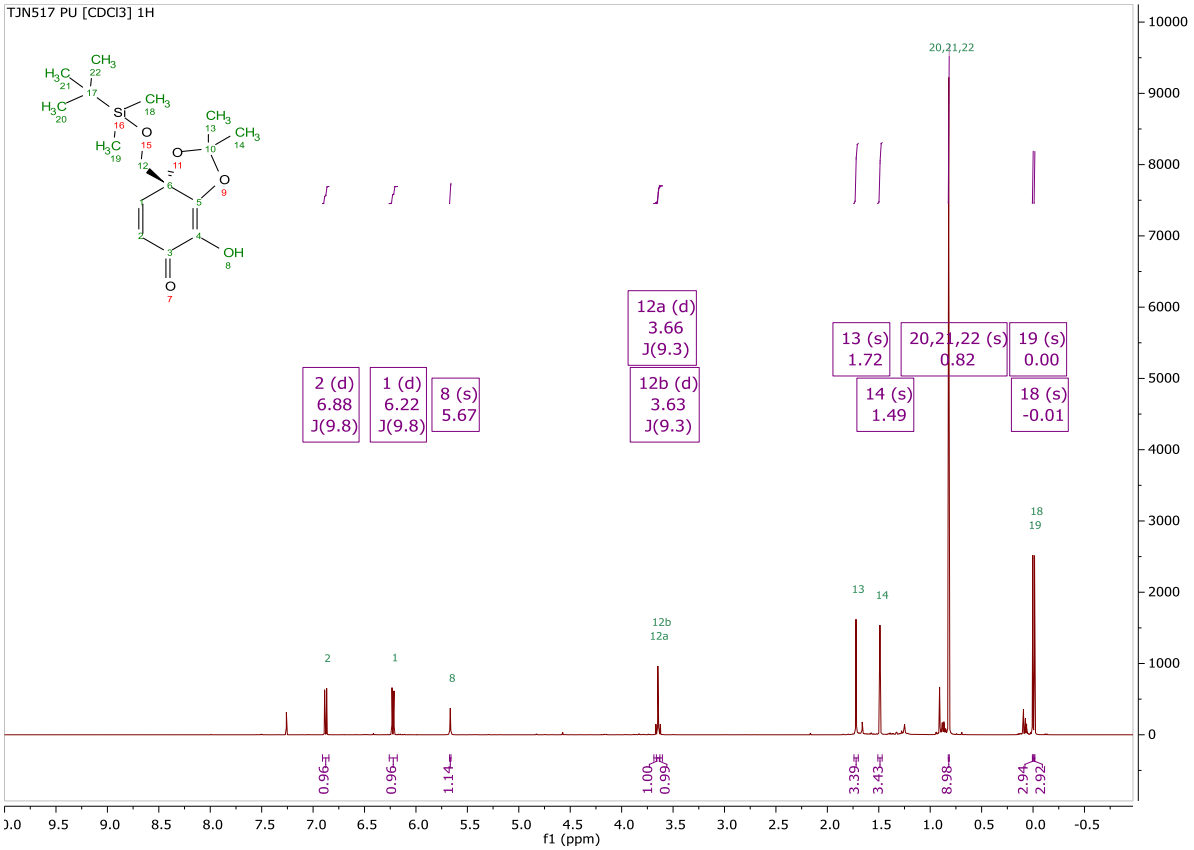
Expected Formula C16 H30 O6 Si1 **Adduct(s):** H, Na

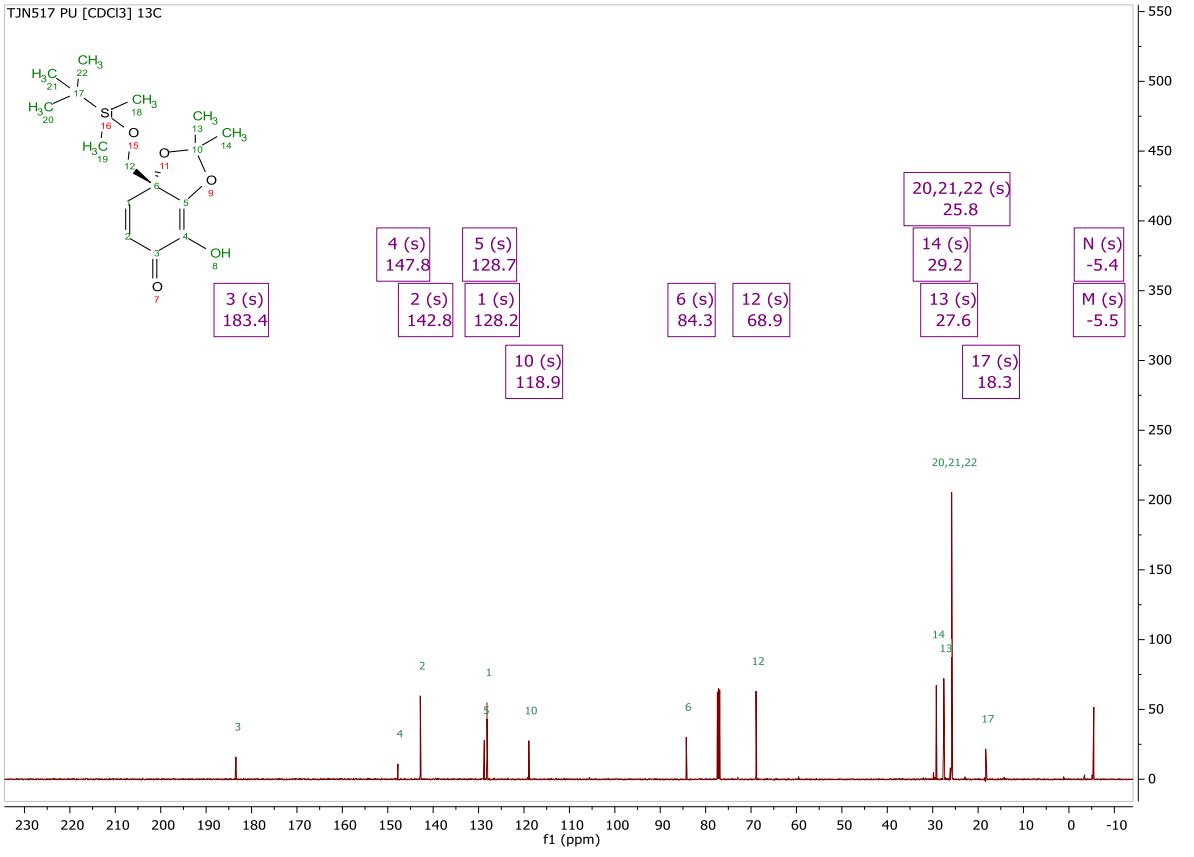
#	meas. m/z	theo. m/z	Err[ppm]	Sigma	Formula
1	389.1740	389.1704	9.70	0.0051	C 16 H 30 Na 1 O 6 Si 1

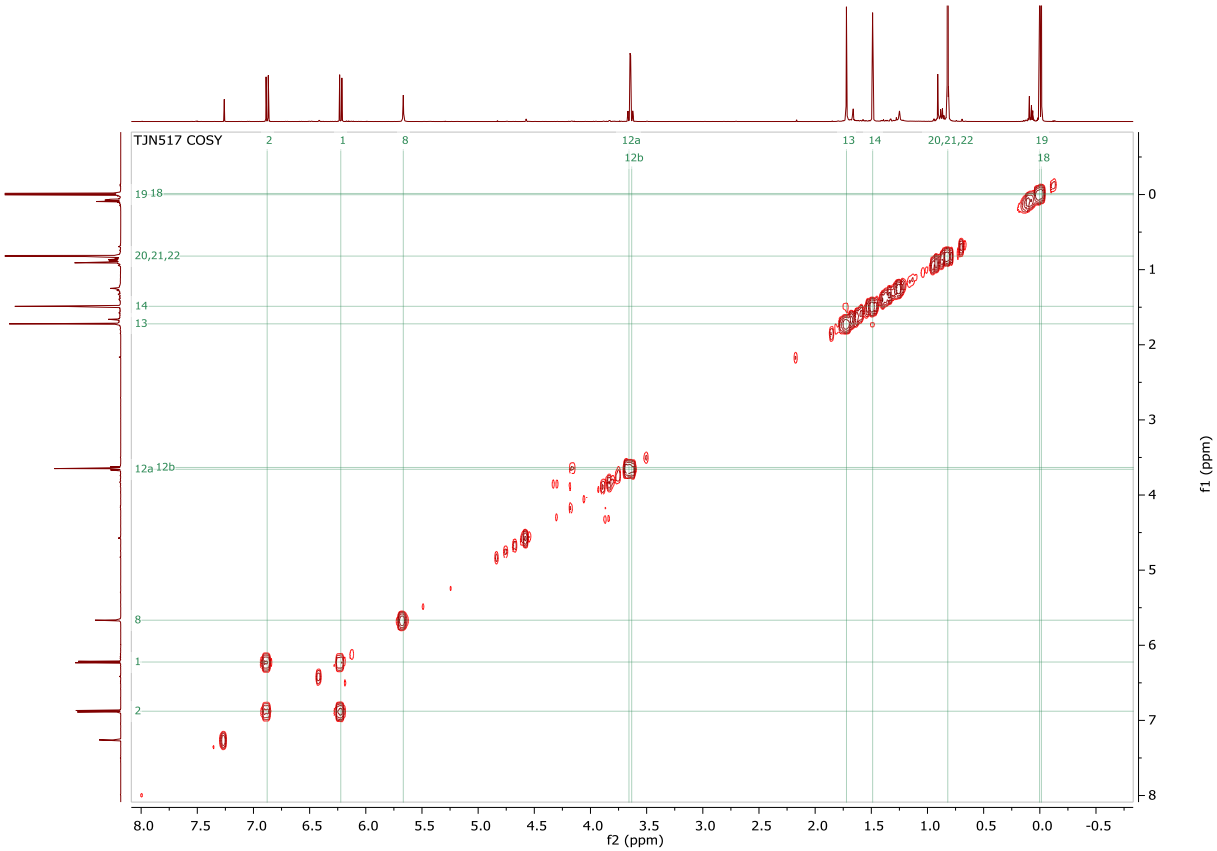
Note: Sigma fits < 0.05 indicates high probability of correct MF.

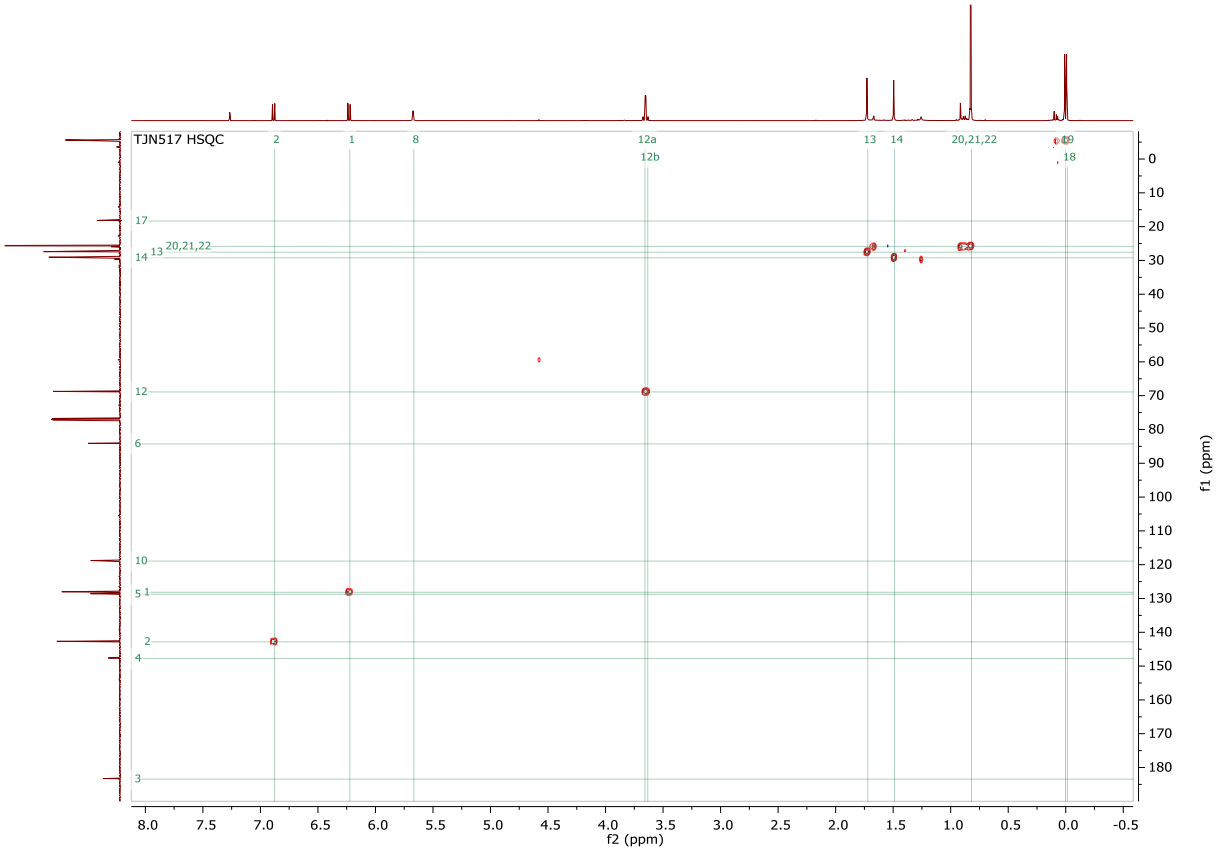
For formula confirmation the mass error / accuracy at 200 Da should be better than 25 ppm, for 500 Da better than 10 ppm and for 1000 Da better than 5 ppm

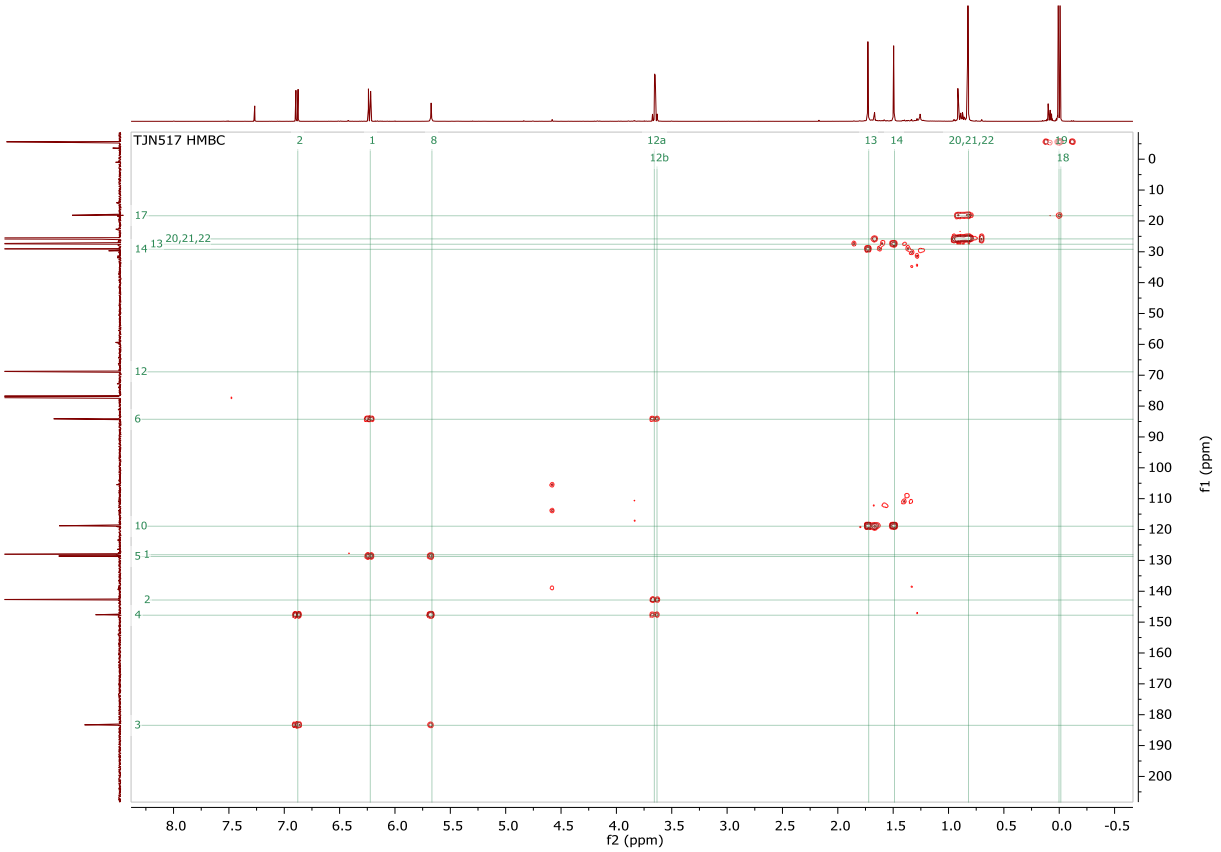
(*R*)-7a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-hydroxy-2,2-dimethylbenzo[d][1,3]dioxol-5(7aH)-one II-45






TJN517 COSY
2
1
8
12a
12b
13
14
20,21,22
19
18
19 18
20,21,22
14
13
12a 12b
8
1
2
f2 (ppm)
f1 (ppm)


TJN517 HSQC
2
1
8
12a
12b
13
14
20,21,22
19
18
17
14
13
20,21,22
12
6
10
5
1
2
4
3
f2 (ppm)
f1 (ppm)

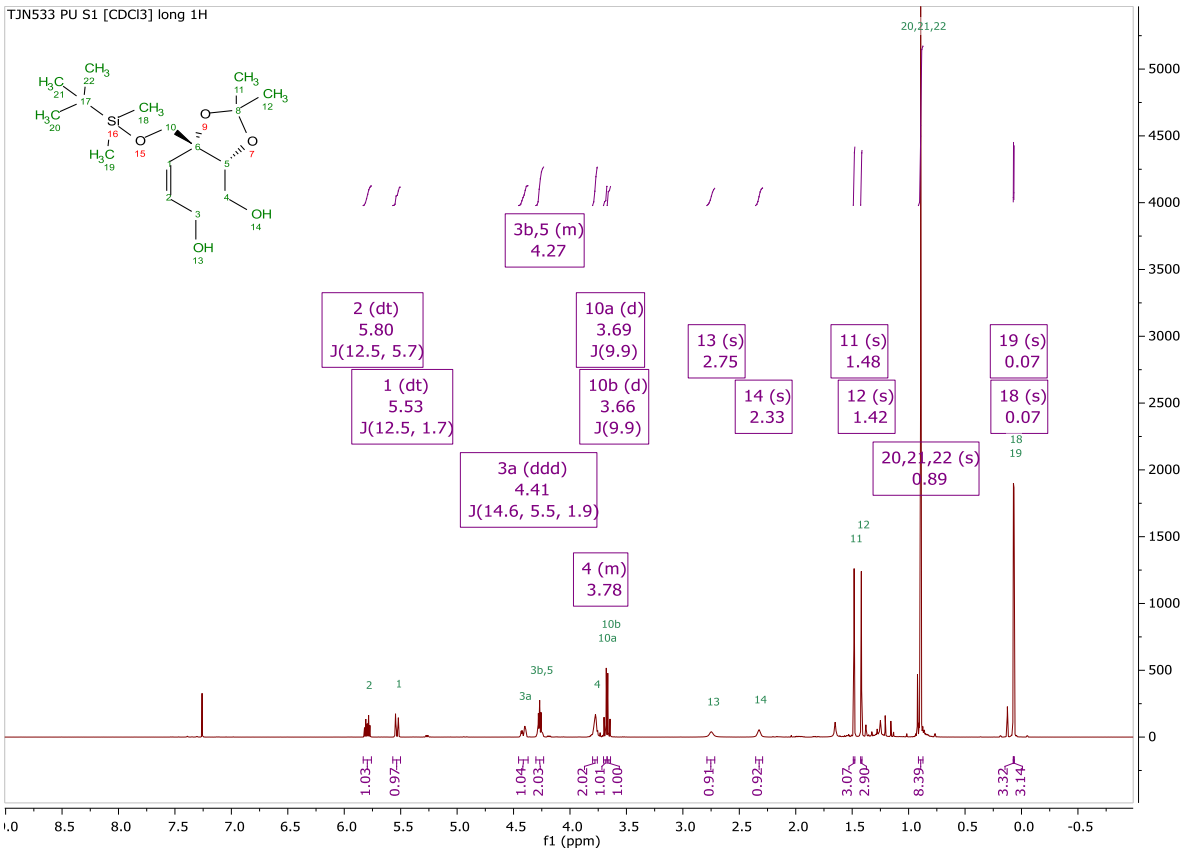


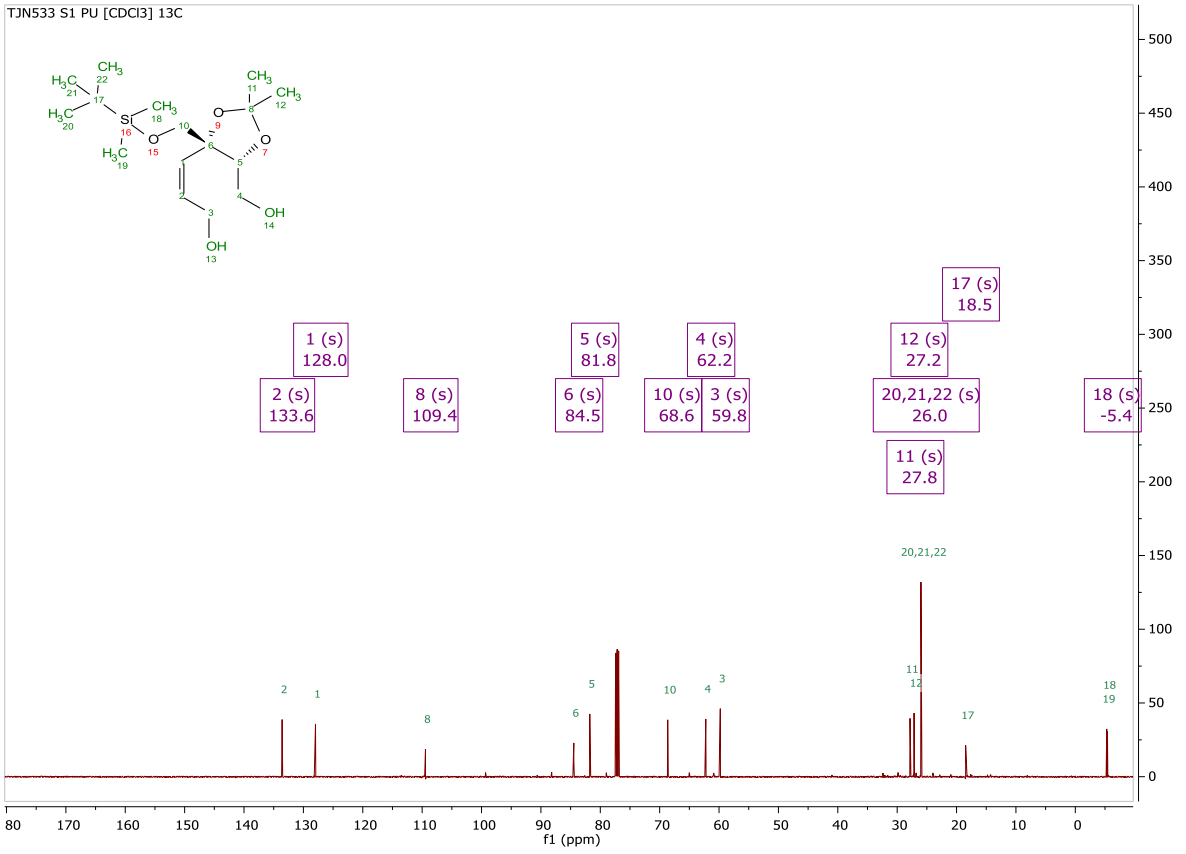
Bruker Daltonics Compass OpenAccess 1.3.0 - Results of job 77115 - Mon Sep 03 15:53:24 BST 2018

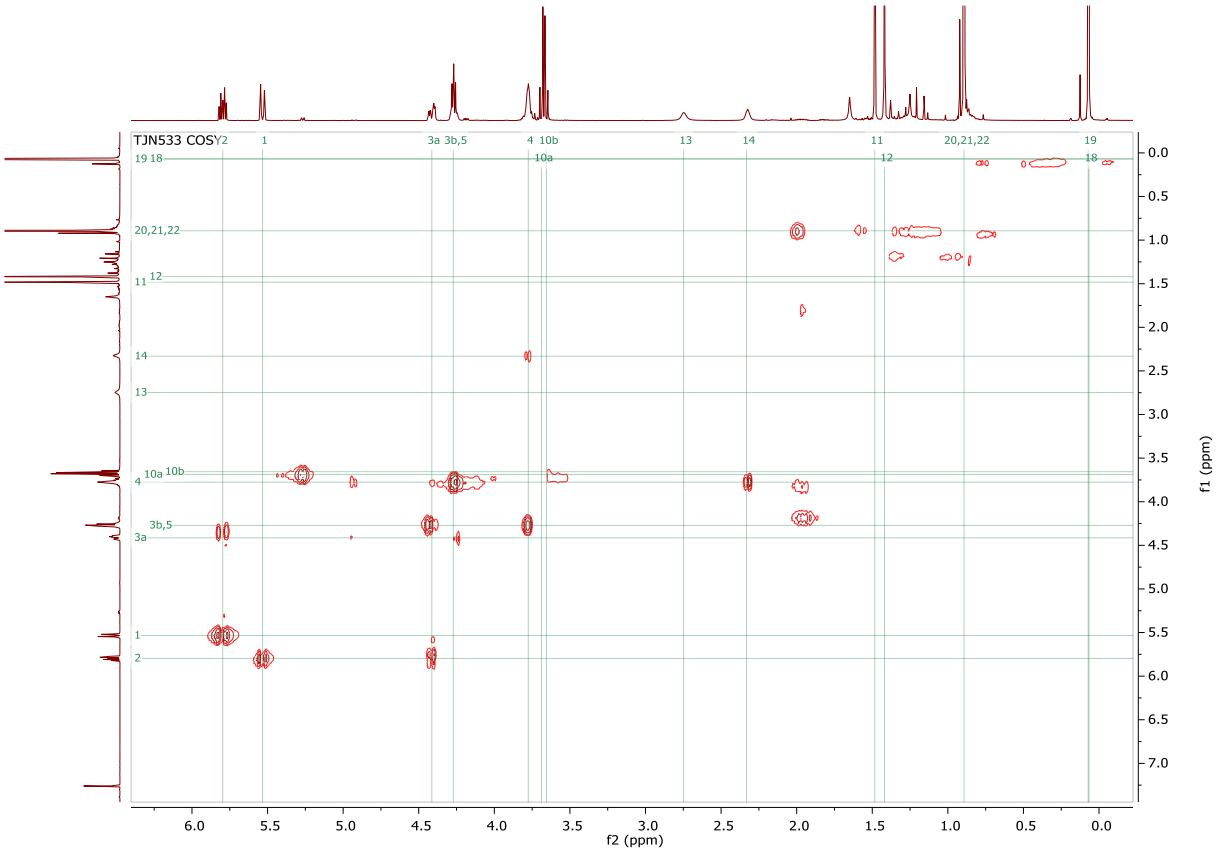
Results of job 77115

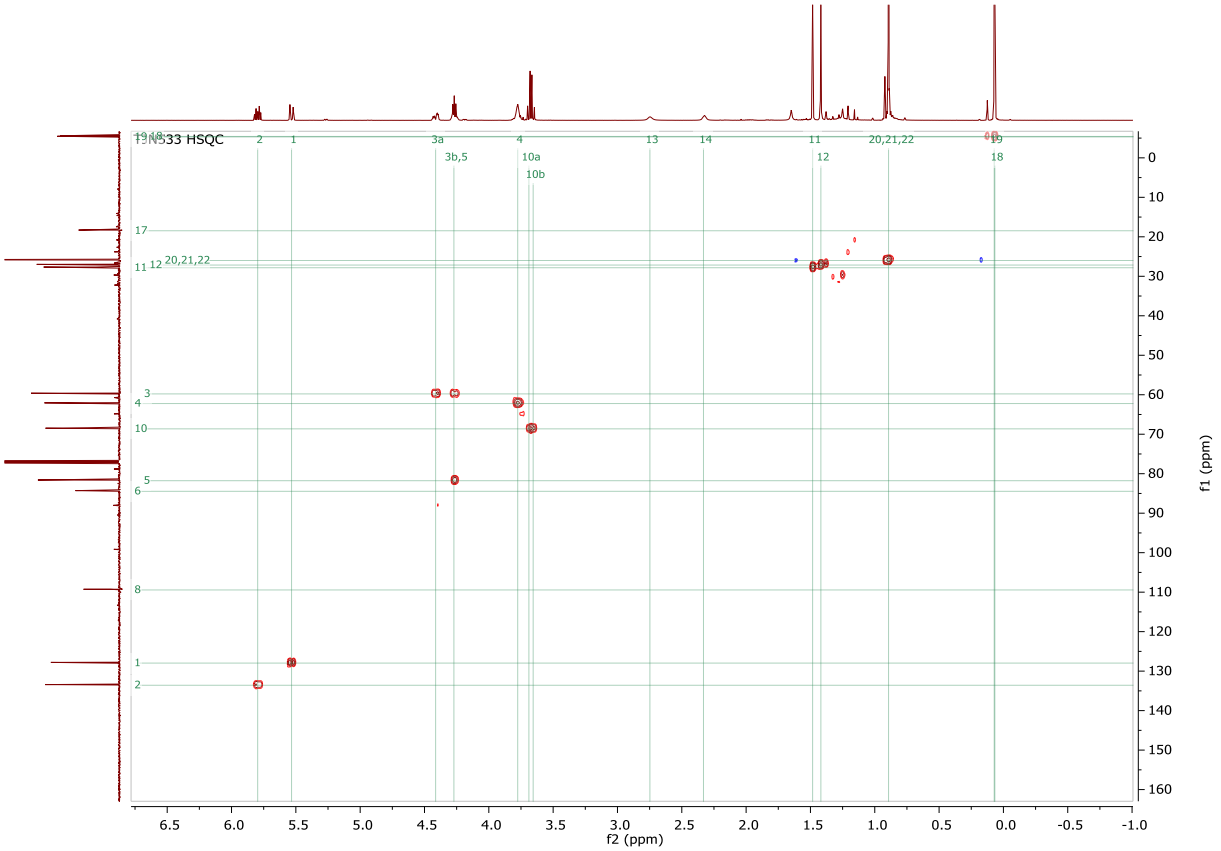
Sample	Sample Description	Method	Submitter	Pos	Expected Formula	Project	Peaknumber	meas. m/z	theo. m/z	err[ppm]	sigma	Formulae
tn_sel_TJN17		Confirm Formula Positive 50to500 loop inj	tjn30 Toby Nash		C16 H26 O5 Si1	TJN517	1	327.165200	327.1622	9.1	0.0141	C 16 H 27 O 5 Si 1

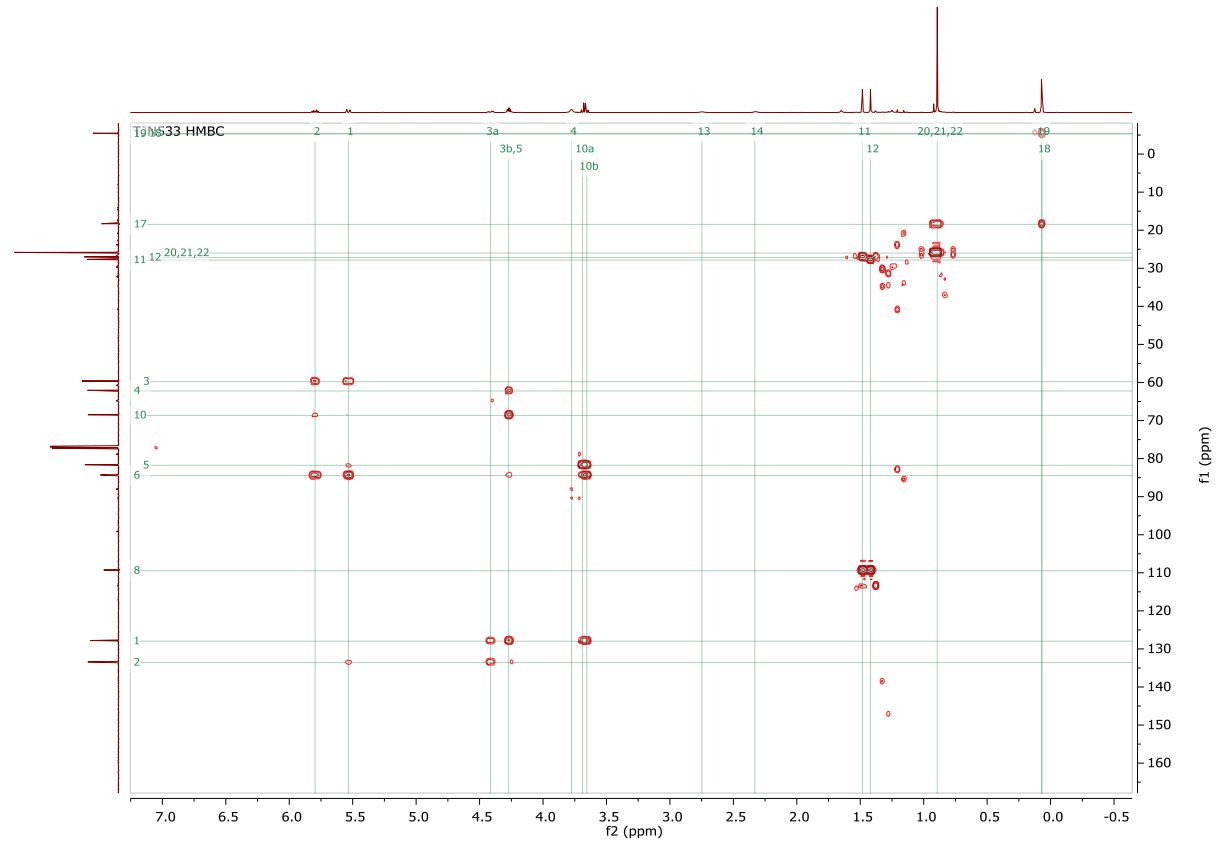
(*Z*)-3-((4*R*,5*R*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol II-47

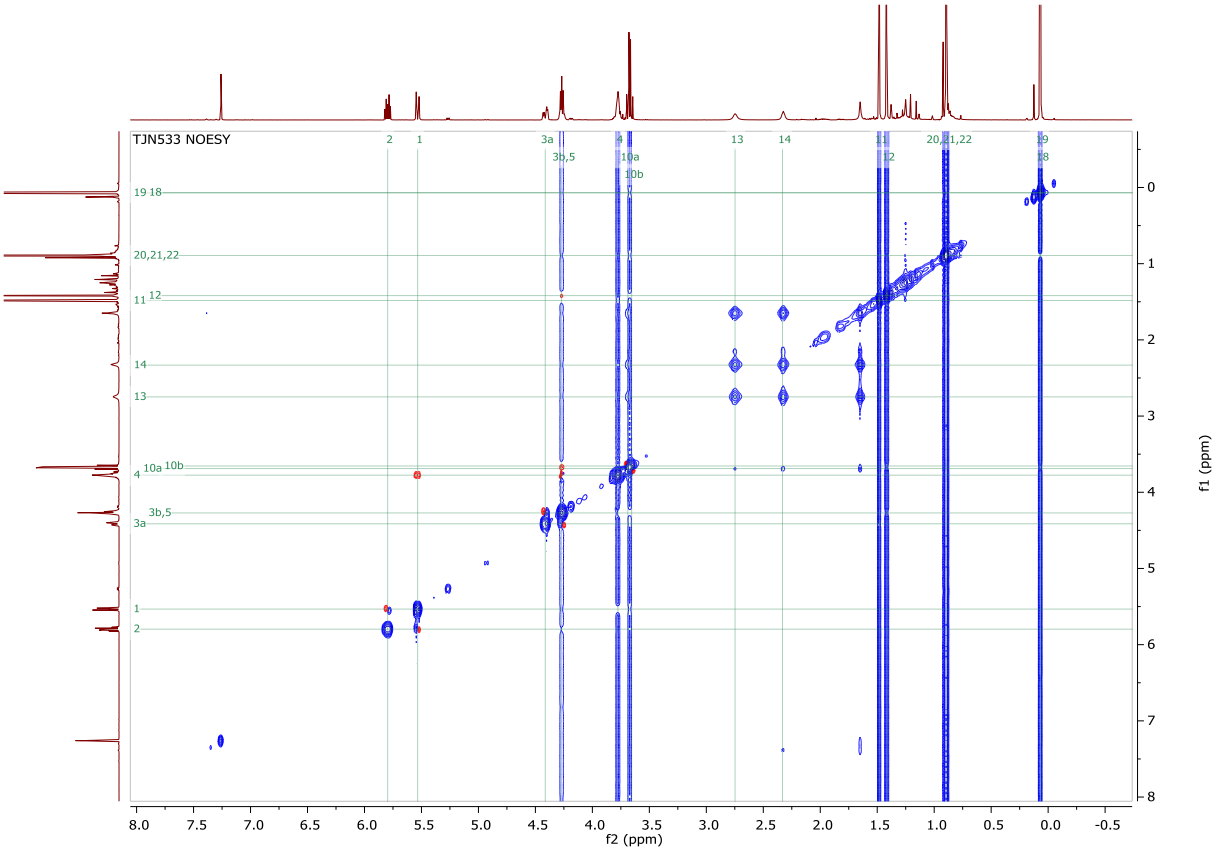





TJN533 COSY
f2 (ppm)
f1 (ppm)


TJN533 HSQC
f2 (ppm)
f1 (ppm)

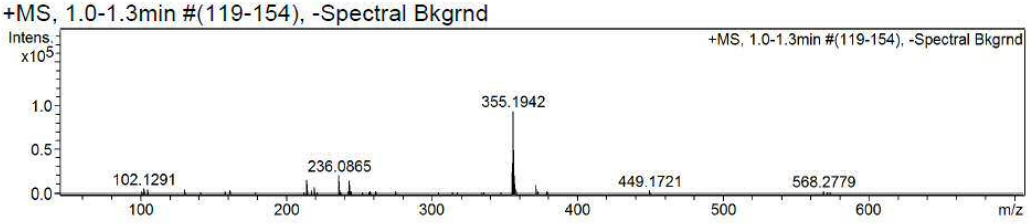

TJN533 HMBC
f2 (ppm)
f1 (ppm)


TJN533 NOESY
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

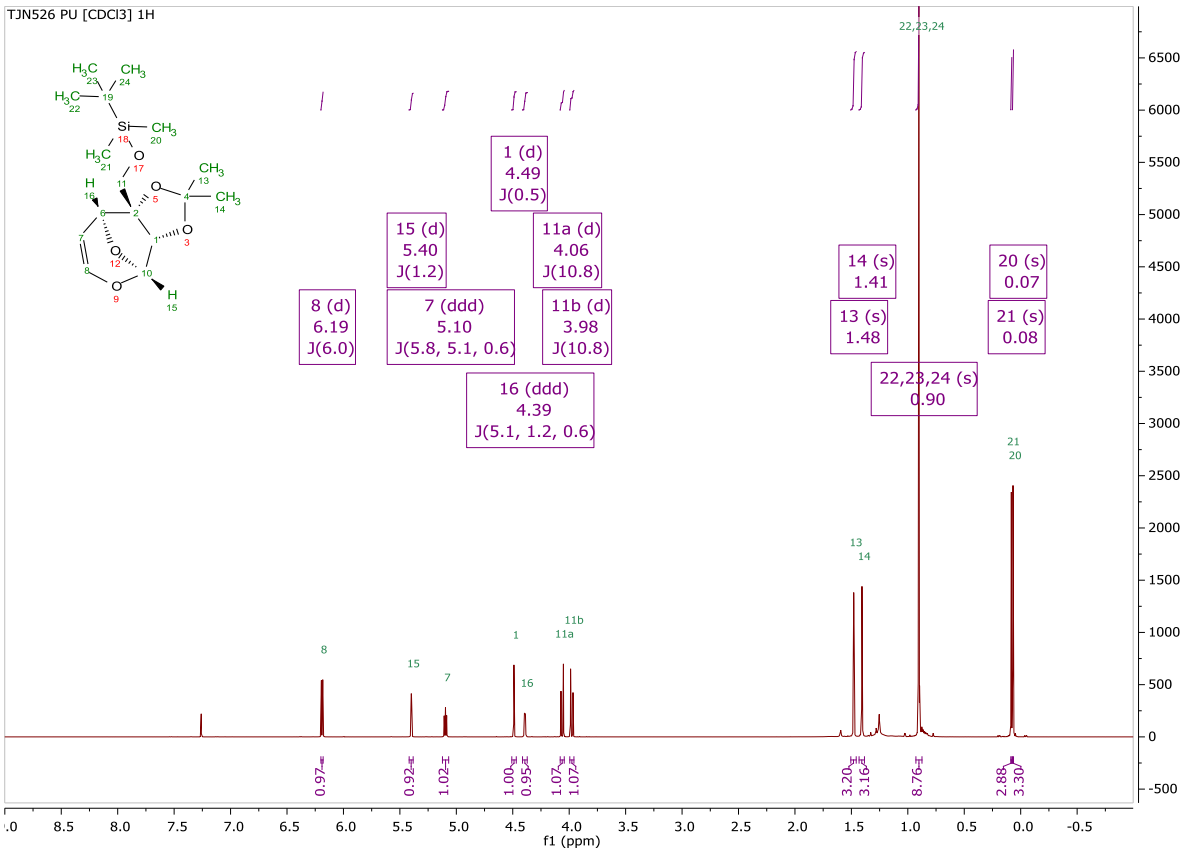
Sample-ID	tn_sel_TJN533	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN533_357645_20_01_63937.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	16/06/2018 11:29:13
Ionisation Mode	positive electrospray (ESI)		

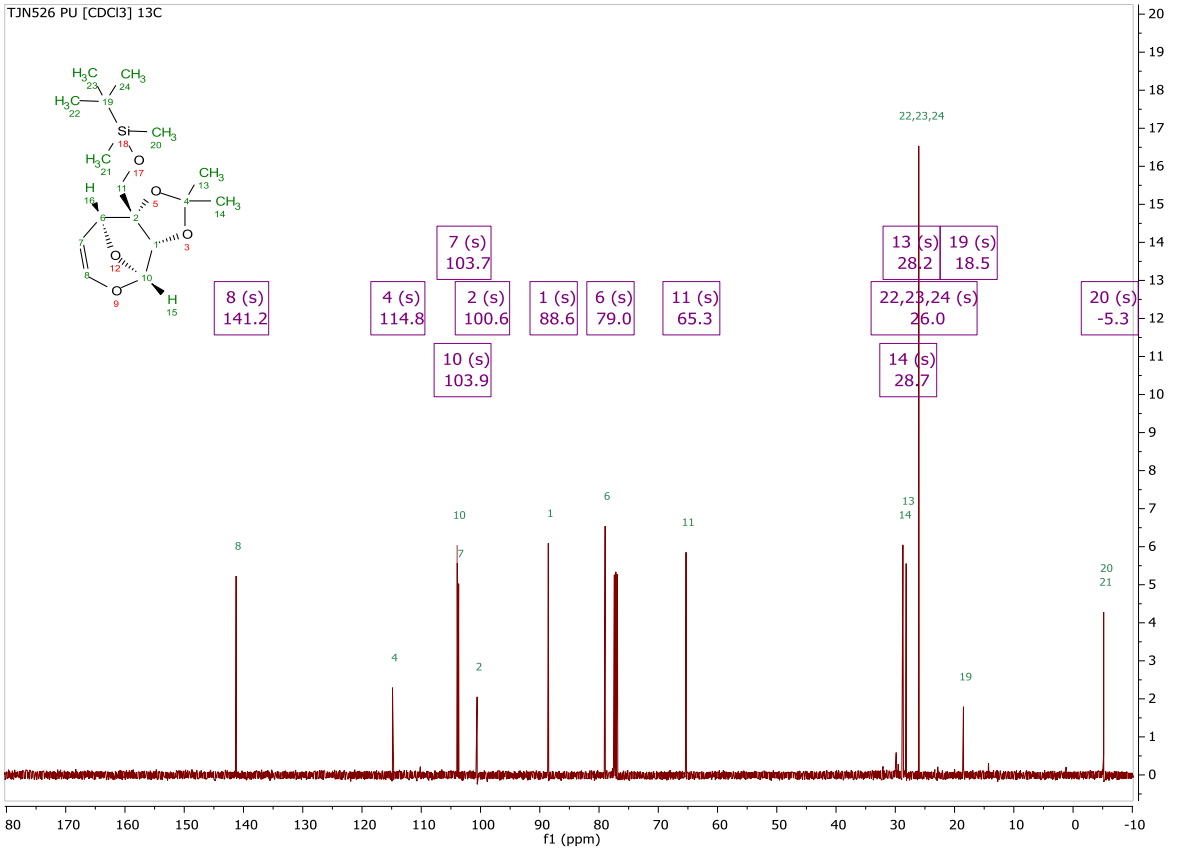
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

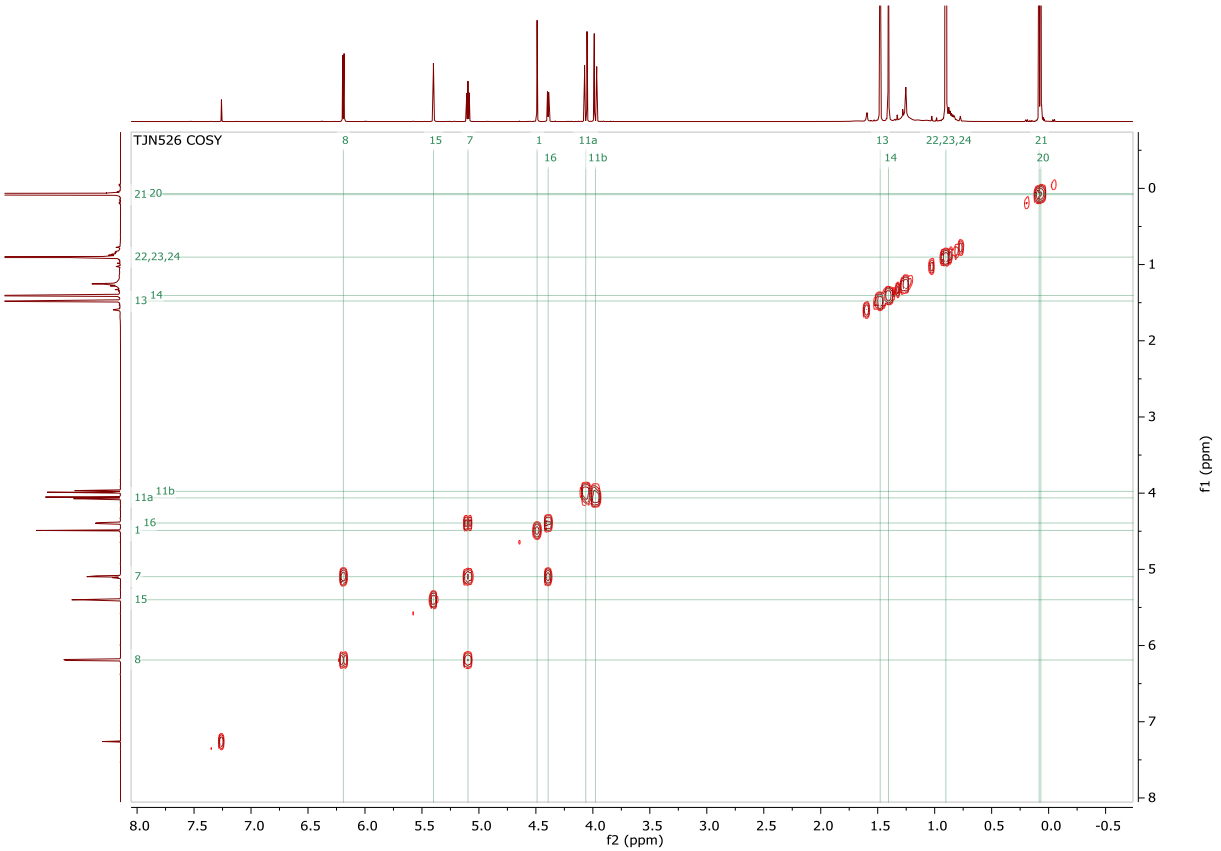


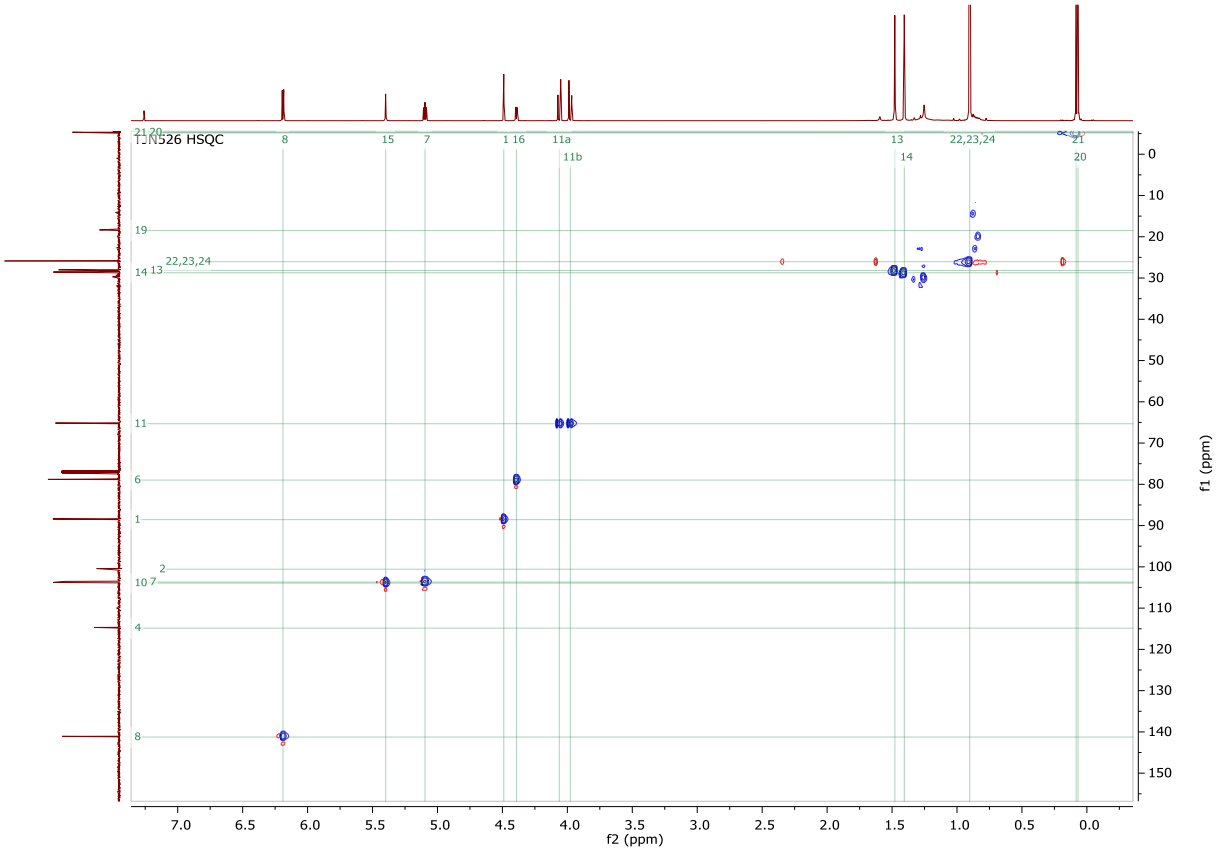
#	m/z	I	I %	Area	S/N
1	102.1291	5492	5.9	114	3632.5
2	130.1613	4815	5.2	117	2081.5
3	214.0928	15941	17.1	471	1425.8
4	219.1383	7225	7.7	280	589.8
5	236.0865	20405	21.8	220	1288.0
6	243.1374	14696	15.7	633	848.7
7	355.1942	93453	100.0	6051	4058.0
8	356.1969	20383	21.8	1286	872.6
9	357.1954	6000	6.4	402	253.3
10	371.1877	9994	10.7	654	353.8

tert-Butyl(((3a*S*,4*S*,8*S*,8a*S*)-2,2-dimethyl-3a,4-dihydro-4,8-epoxy[1,3]dioxolo[4,5-c]oxepin-8a(8H)-yl)methoxy)dimethylsilane II-48






TJN526 COSY
f2 (ppm)
f1 (ppm)

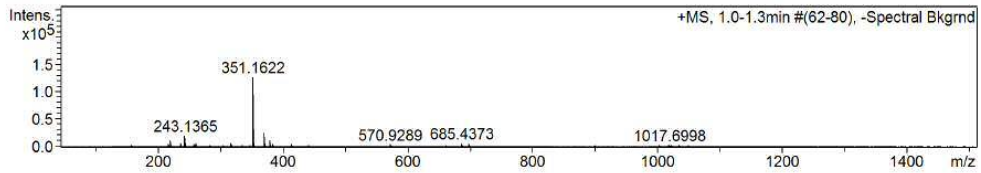

TJN526 HSQC
f2 (ppm)
f1 (ppm)

Generate Molecular Formula for Unknowns

Sample ID	tn_sel_TJN526	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN526_357644_19_01_63936.d	Supervisor	sl288 Simon Lewis
Method used	Find Formula Positive 50to1500 loop inj.m	Acquisition Date	16/06/2018 11:25:42
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(62-80), -Spectral Bkgrnd

No of Most Intense MS Peaks Analysed



#	m/z	I	I %	Area	S/N
1	219.1355	10410	8.2	306	355.9
2	236.0725	5921	4.7	75	174.0
3	243.1365	20568	16.2	736	571.2
4	316.9296	5576	4.4	252	107.4
5	351.1622	126859	100.0	6117	2279.5
6	352.1633	30556	24.1	1618	547.9
7	353.1619	8904	7.0	453	159.3
8	369.1706	24490	19.3	1253	424.8
9	379.1146	10865	8.6	570	184.9
10	685.4373	6871	5.4	745	96.1

Crystal structure data for II-48

Table 1. Crystal data and structure refinement for s18sel8.

Identification code	s18sel8	
Empirical formula	C16 H28 O5 Si	
Formula weight	328.47	
Temperature	149.9(4) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.96710(10) Å	α= 90°.
	b = 8.28570(10) Å	β= 90°.
	c = 26.8889(2) Å	γ = 90°.
Volume	1775.02(3) $Å^3$	
Z	4	
Density (calculated)	1.229 Mg/m^3	
Absorption coefficient	1.340 mm^{-1}	
F(000)	712	
Crystal size	0.220 x 0.200 x 0.080 mm^3	
Theta range for data collection	3.287 to 73.054°.	
Index ranges	-9<=h<=7, -10<=k<=10, -33<=l<=33	
Reflections collected	35371	
Independent reflections	3550 [R(int) = 0.0345]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.86421	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3550 / 0 / 206	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0246, wR2 = 0.0657	
R indices (all data)	R1 = 0.0247, wR2 = 0.0659	
Absolute structure parameter	0.003(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.205 and -0.241 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for s18sel8. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si	6554(1)	5542(1)	3300(1)	17(1)
O(1)	3528(2)	3495(1)	3914(1)	19(1)
O(2)	2993(2)	1969(1)	4608(1)	23(1)
O(3)	1536(2)	5461(1)	4557(1)	20(1)
O(4)	2517(2)	5545(2)	5377(1)	24(1)
O(5)	6452(2)	5785(1)	3909(1)	21(1)
C(1)	2779(2)	2019(2)	4078(1)	21(1)
C(2)	943(3)	2013(3)	3940(1)	30(1)
C(3)	3729(3)	604(2)	3857(1)	32(1)
C(4)	3503(2)	3502(2)	4786(1)	18(1)
C(5)	2021(2)	4528(2)	4970(1)	20(1)
C(6)	3527(2)	6804(2)	5227(1)	24(1)
C(7)	3899(2)	7092(2)	4755(1)	21(1)
C(8)	3143(2)	6009(2)	4365(1)	17(1)
C(9)	4137(2)	4430(2)	4323(1)	16(1)
C(10)	6027(2)	4645(2)	4283(1)	20(1)
C(11)	4504(2)	6054(3)	3007(1)	30(1)
C(12)	7129(3)	3425(2)	3143(1)	29(1)
C(13)	8210(2)	7015(2)	3090(1)	22(1)
C(14)	8354(3)	6991(3)	2519(1)	35(1)
C(15)	9914(2)	6565(3)	3313(1)	35(1)
C(16)	7741(3)	8735(2)	3254(1)	32(1)

Table 3. Bond lengths [Å] for s18sel8.

Si-O(5)	1.6542(11)
Si-C(12)	1.861(2)
Si-C(11)	1.8620(19)
Si-C(13)	1.8843(18)
O(1)-C(1)	1.4303(19)
O(1)-C(9)	1.4311(18)
O(2)-C(4)	1.4159(19)
O(2)-C(1)	1.4382(19)
O(3)-C(5)	1.409(2)
O(3)-C(8)	1.4525(19)
O(4)-C(6)	1.378(2)
O(4)-C(5)	1.4353(19)
O(5)-C(10)	1.4191(19)
C(1)-C(2)	1.509(3)
C(1)-C(3)	1.516(2)
C(2)-H(2A)	0.9800
C(2)-H(2B)	0.9800
C(2)-H(2C)	0.9800
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-C(5)	1.537(2)
C(4)-C(9)	1.546(2)
C(4)-H(4)	1.0000
C(5)-H(5)	1.0000
C(6)-C(7)	1.324(2)
C(6)-H(6)	0.9500
C(7)-C(8)	1.506(2)
C(7)-H(7)	0.9500
C(8)-C(9)	1.534(2)
C(8)-H(8)	1.0000
C(9)-C(10)	1.520(2)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800

C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-C(15)	1.531(3)
C(13)-C(16)	1.539(3)
C(13)-C(14)	1.539(2)
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800

Table 4. Bond angles [°] for s18sel8.

O(5)-Si-C(12)	110.58(8)
O(5)-Si-C(11)	110.41(8)
C(12)-Si-C(11)	109.56(10)
O(5)-Si-C(13)	104.64(7)
C(12)-Si-C(13)	111.70(9)
C(11)-Si-C(13)	109.86(9)
C(1)-O(1)-C(9)	111.55(11)
C(4)-O(2)-C(1)	110.00(12)
C(5)-O(3)-C(8)	102.08(12)
C(6)-O(4)-C(5)	112.48(12)
C(10)-O(5)-Si	129.21(10)
O(1)-C(1)-O(2)	106.31(12)
O(1)-C(1)-C(2)	109.35(14)
O(2)-C(1)-C(2)	110.95(15)
O(1)-C(1)-C(3)	109.44(14)
O(2)-C(1)-C(3)	107.91(14)
C(2)-C(1)-C(3)	112.68(16)
C(1)-C(2)-H(2A)	109.5
C(1)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5
C(1)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
C(1)-C(3)-H(3A)	109.5
C(1)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(1)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
O(2)-C(4)-C(5)	112.61(14)
O(2)-C(4)-C(9)	105.62(12)
C(5)-C(4)-C(9)	103.66(13)
O(2)-C(4)-H(4)	111.5
C(5)-C(4)-H(4)	111.5
C(9)-C(4)-H(4)	111.5
O(3)-C(5)-O(4)	110.77(13)
O(3)-C(5)-C(4)	105.00(12)

O(4)-C(5)-C(4)	111.07(13)
O(3)-C(5)-H(5)	110.0
O(4)-C(5)-H(5)	110.0
C(4)-C(5)-H(5)	110.0
C(7)-C(6)-O(4)	123.20(15)
C(7)-C(6)-H(6)	118.4
O(4)-C(6)-H(6)	118.4
C(6)-C(7)-C(8)	118.02(15)
C(6)-C(7)-H(7)	121.0
C(8)-C(7)-H(7)	121.0
O(3)-C(8)-C(7)	107.00(13)
O(3)-C(8)-C(9)	102.40(12)
C(7)-C(8)-C(9)	110.67(13)
O(3)-C(8)-H(8)	112.1
C(7)-C(8)-H(8)	112.1
C(9)-C(8)-H(8)	112.1
O(1)-C(9)-C(10)	110.17(13)
O(1)-C(9)-C(8)	110.06(12)
C(10)-C(9)-C(8)	114.62(14)
O(1)-C(9)-C(4)	103.81(12)
C(10)-C(9)-C(4)	116.05(13)
C(8)-C(9)-C(4)	101.31(12)
O(5)-C(10)-C(9)	111.40(13)
O(5)-C(10)-H(10A)	109.3
C(9)-C(10)-H(10A)	109.3
O(5)-C(10)-H(10B)	109.3
C(9)-C(10)-H(10B)	109.3
H(10A)-C(10)-H(10B)	108.0
Si-C(11)-H(11A)	109.5
Si-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
Si-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
Si-C(12)-H(12A)	109.5
Si-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
Si-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5

H(12B)-C(12)-H(12C)	109.5
C(15)-C(13)-C(16)	109.11(16)
C(15)-C(13)-C(14)	108.85(16)
C(16)-C(13)-C(14)	108.48(16)
C(15)-C(13)-Si	110.22(13)
C(16)-C(13)-Si	110.08(12)
C(14)-C(13)-Si	110.06(13)
C(13)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(13)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(13)-C(15)-H(15A)	109.5
C(13)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(13)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(13)-C(16)-H(16A)	109.5
C(13)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(13)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5

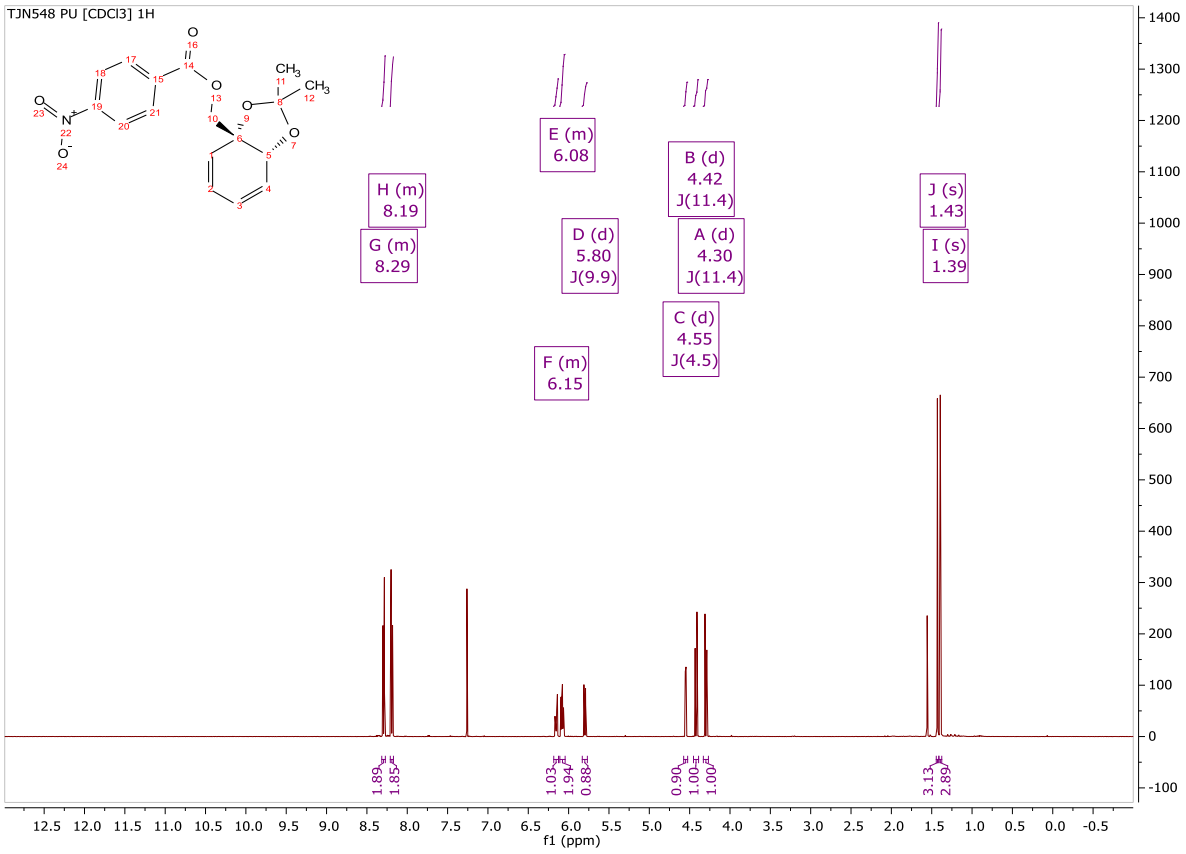
Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for s18sel8. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

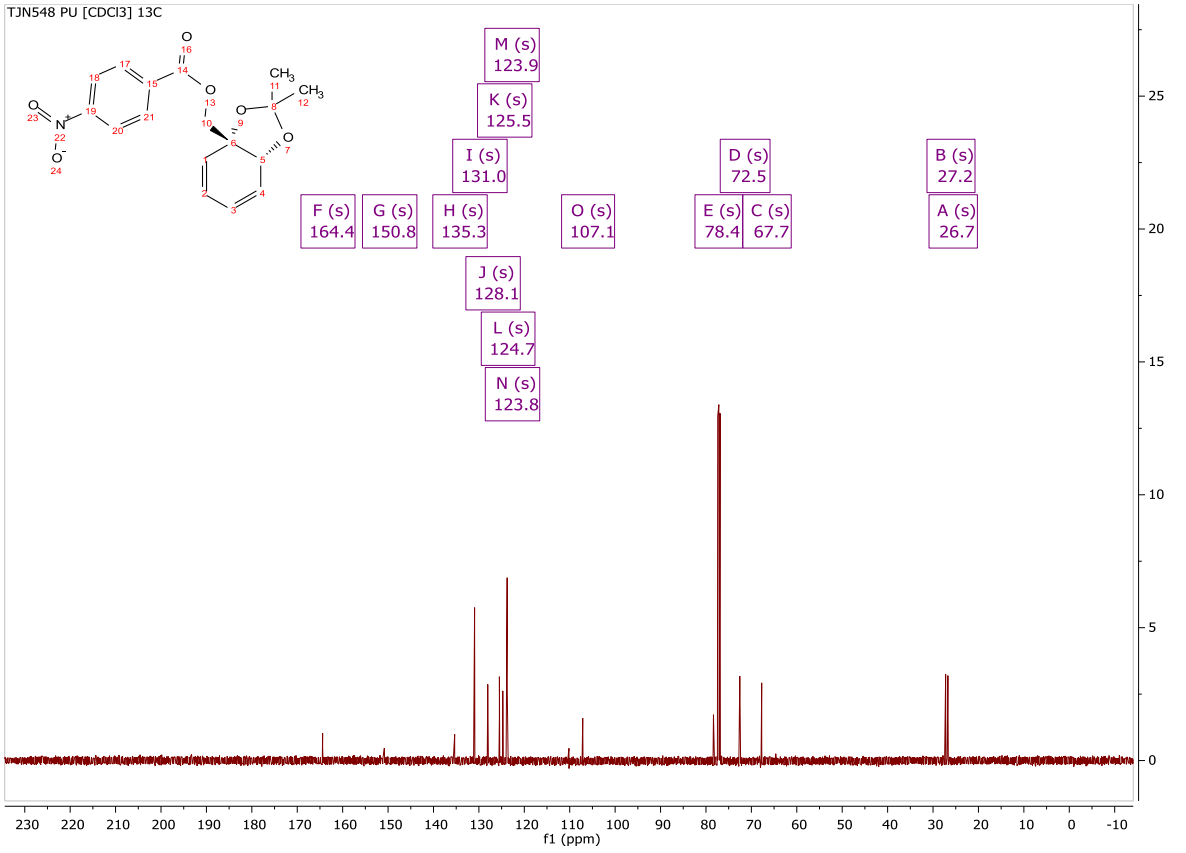
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si	14(1)	23(1)	15(1)	0(1)	0(1)	1(1)
O(1)	26(1)	17(1)	13(1)	1(1)	-1(1)	-3(1)
O(2)	40(1)	15(1)	15(1)	1(1)	-1(1)	-3(1)
O(3)	16(1)	22(1)	23(1)	0(1)	0(1)	1(1)
O(4)	29(1)	24(1)	18(1)	-4(1)	4(1)	-2(1)
O(5)	22(1)	24(1)	16(1)	1(1)	2(1)	-3(1)
C(1)	31(1)	16(1)	15(1)	1(1)	1(1)	-3(1)
C(2)	31(1)	35(1)	23(1)	1(1)	0(1)	-10(1)
C(3)	52(1)	21(1)	24(1)	-4(1)	-1(1)	7(1)
C(4)	23(1)	16(1)	15(1)	1(1)	-1(1)	-2(1)
C(5)	21(1)	20(1)	18(1)	-1(1)	3(1)	-3(1)
C(6)	24(1)	22(1)	26(1)	-6(1)	0(1)	-1(1)
C(7)	22(1)	16(1)	26(1)	-1(1)	-1(1)	-2(1)
C(8)	17(1)	17(1)	18(1)	2(1)	1(1)	0(1)
C(9)	19(1)	16(1)	12(1)	1(1)	-1(1)	1(1)
C(10)	18(1)	24(1)	16(1)	2(1)	1(1)	2(1)
C(11)	20(1)	44(1)	26(1)	8(1)	-4(1)	0(1)
C(12)	31(1)	29(1)	28(1)	-7(1)	2(1)	1(1)
C(13)	20(1)	29(1)	18(1)	0(1)	3(1)	-2(1)
C(14)	40(1)	46(1)	21(1)	2(1)	10(1)	-8(1)
C(15)	16(1)	50(1)	39(1)	2(1)	2(1)	-2(1)
C(16)	37(1)	27(1)	32(1)	-1(1)	5(1)	-4(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for s18sel8.

	x	y	z	U(eq)
H(2A)	829	2057	3578	45
H(2B)	391	2954	4089	45
H(2C)	417	1024	4065	45
H(3A)	3673	657	3493	49
H(3B)	3223	-408	3971	49
H(3C)	4904	648	3963	49
H(4)	4398	3405	5044	21
H(5)	1076	3811	5075	24
H(6)	3978	7500	5474	29
H(7)	4621	7957	4665	26
H(8)	3027	6566	4037	21
H(10A)	6476	5014	4607	23
H(10B)	6553	3594	4203	23
H(11A)	4597	5947	2645	45
H(11B)	4200	7167	3091	45
H(11C)	3636	5317	3130	45
H(12A)	7338	3339	2784	44
H(12B)	6208	2702	3236	44
H(12C)	8145	3119	3325	44
H(14A)	7270	7284	2372	53
H(14B)	8673	5907	2408	53
H(14C)	9210	7768	2413	53
H(15A)	10280	5523	3179	52
H(15B)	9813	6489	3676	52
H(15C)	10741	7396	3228	52
H(16A)	8604	9493	3141	48
H(16B)	7664	8774	3618	48
H(16C)	6655	9033	3109	48

((3a*R*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methyl 4-nitrobenzoate II-50

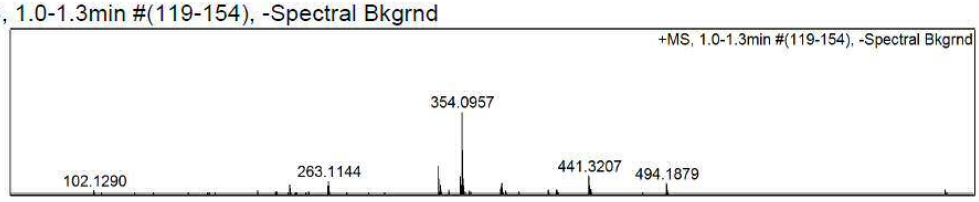




Confirmation of Expected Formula

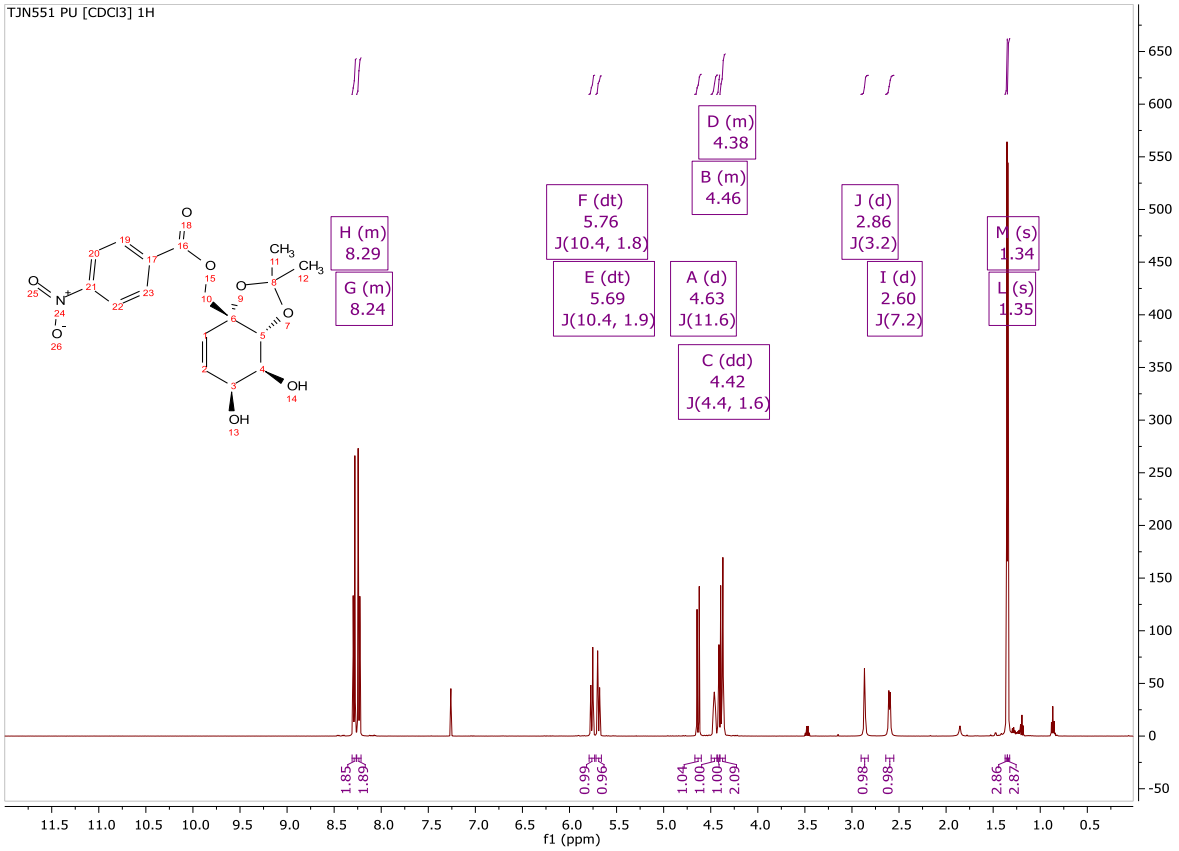
Sample-ID	tn_sel_TJN548	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN548_358750_48_01_65166.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	11/09/2018 17:12:10
Ionisation Mode	positive electrospray (ESI)		

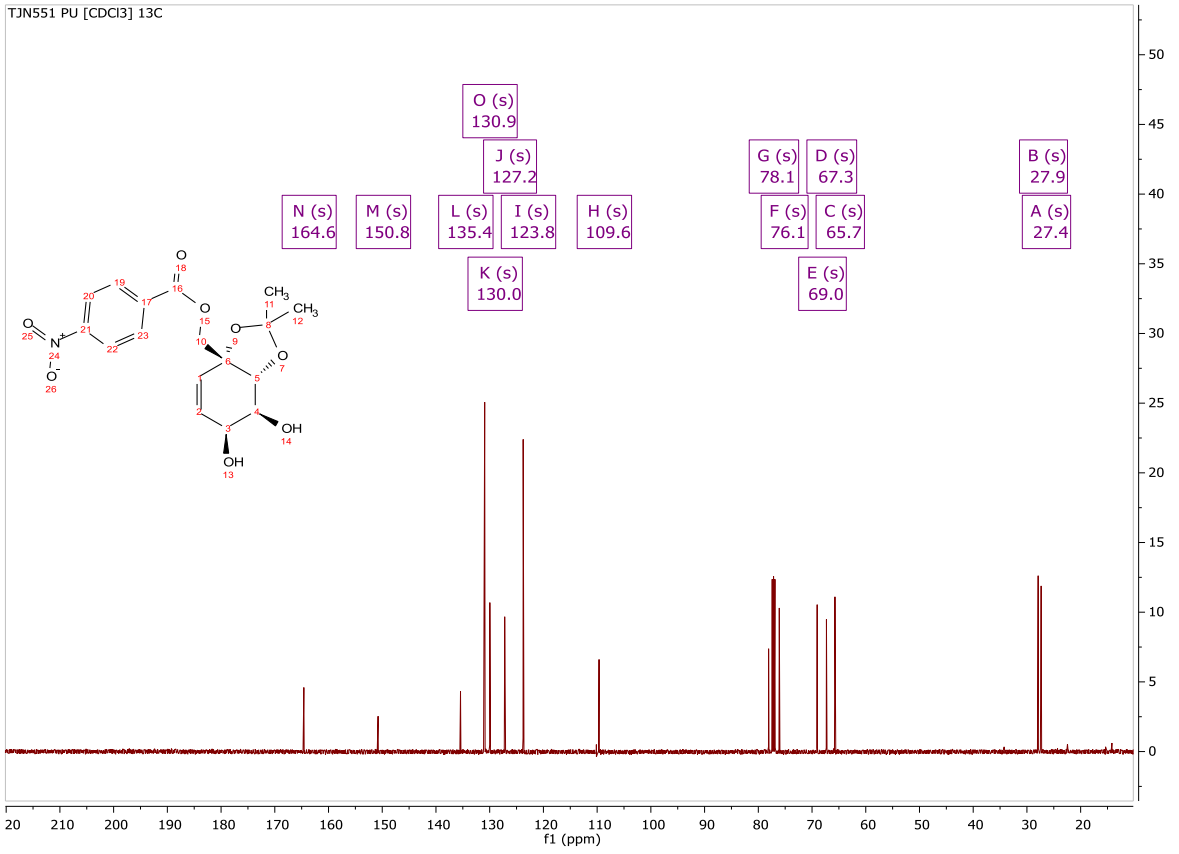
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

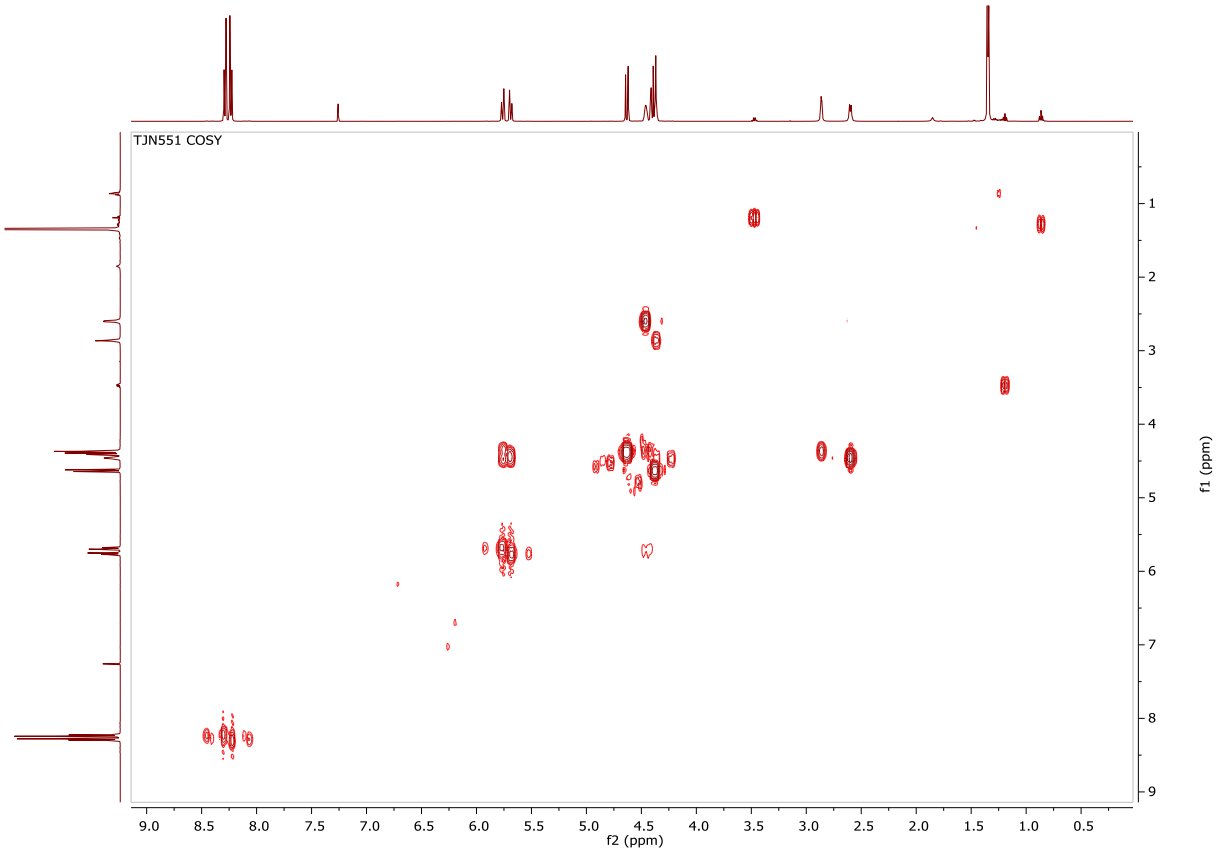


#	m/z	I	I %	Area	S/N
1	236.0759	10192	10.4	146	661.2
2	263.1144	15447	15.7	206	1121.0
3	338.2318	32664	33.3	1035	1243.2
4	339.2283	10231	10.4	366	381.8
5	353.2670	21010	21.4	1295	615.7
6	354.0957	98211	100.0	6111	2842.0
7	355.0984	18440	18.8	1087	525.6
8	381.2979	12788	13.0	825	317.1
9	441.3207	21788	22.2	729	1686.6
10	494.1879	12680	12.9	1146	1189.4

((3a*R*,6*S*,7*S*,7a*R*)-6,7-Dihydroxy-2,2-dimethyl-7,7a-dihydrobenzo[d][1,3]dioxol-3a(6H)-yl)methyl 4-nitrobenzoate II-51





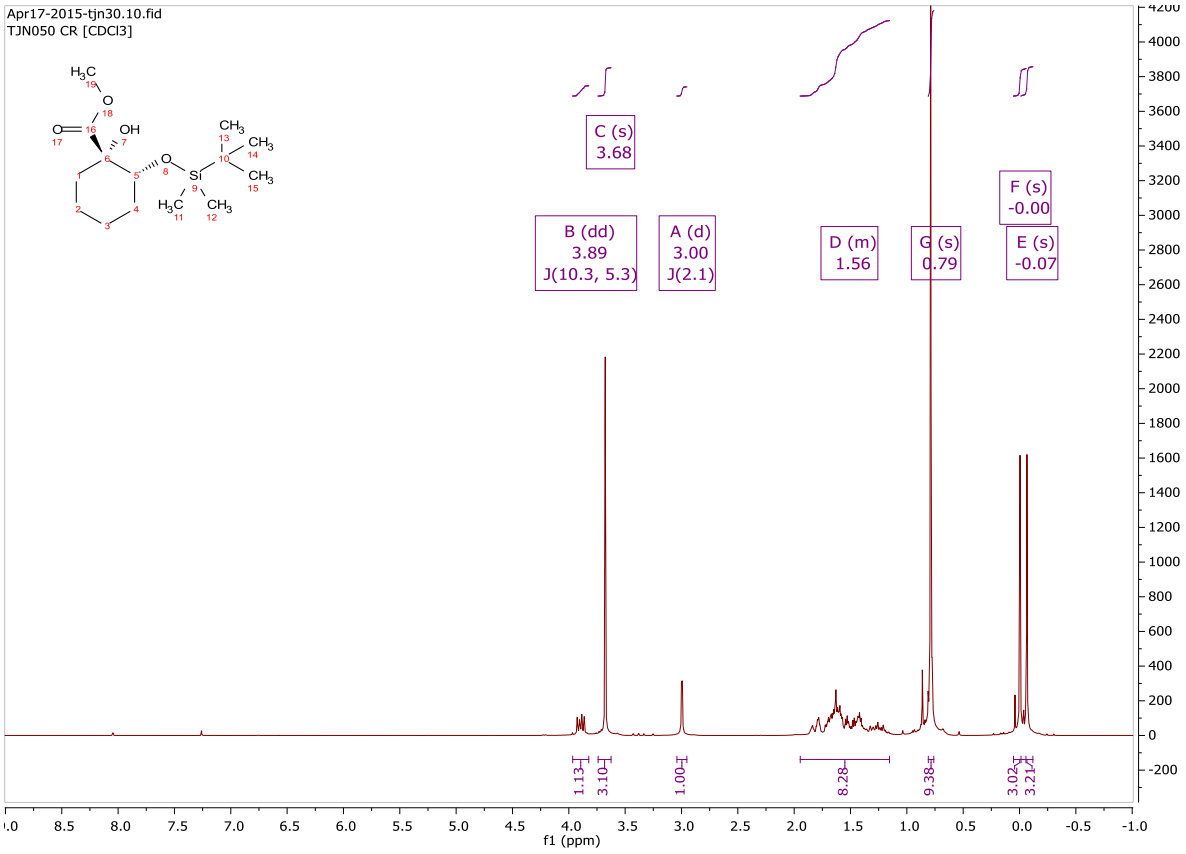


Bruker Daltonics Compass OpenAccess 1.3.0 - Results of job 77347 - Fri Sep 14 14:36:05 BST 2018

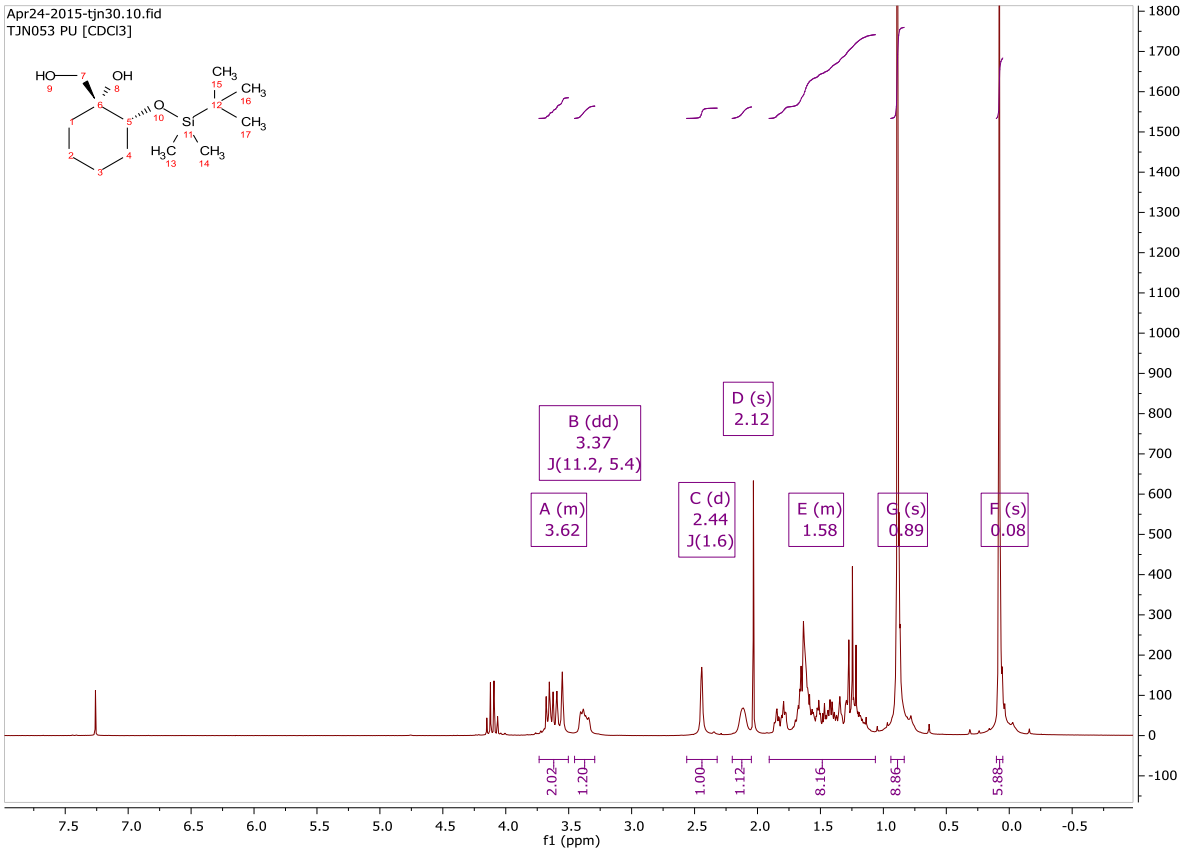
Results of job 77347

Sample	Sample Description	Method	Submitter	Pos	Expected Formula	Project	Peaknumber	meas. m/z	theo. m/z	err[ppm]	sigma	Formulae
tn_sel_TJN551		Confirm Formula Positive 50to500 loop inj	tjn30 Toby Nash		C17 H19 N1 O8	TJN551	1	388.102500	388.1003	5.7	0.0038	C 17 H 19 N 1 Na 1 O 8

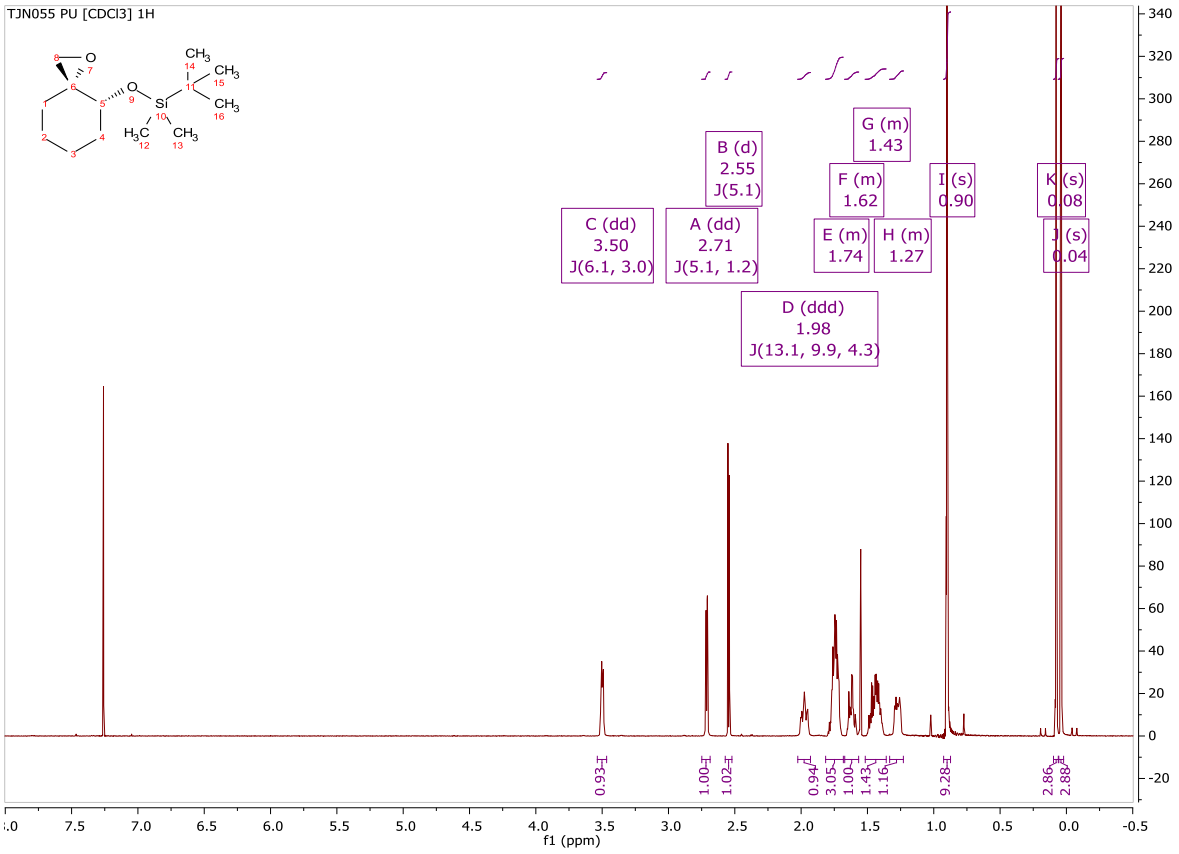
Methyl (1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxycyclohexane-1-carboxylate II-52

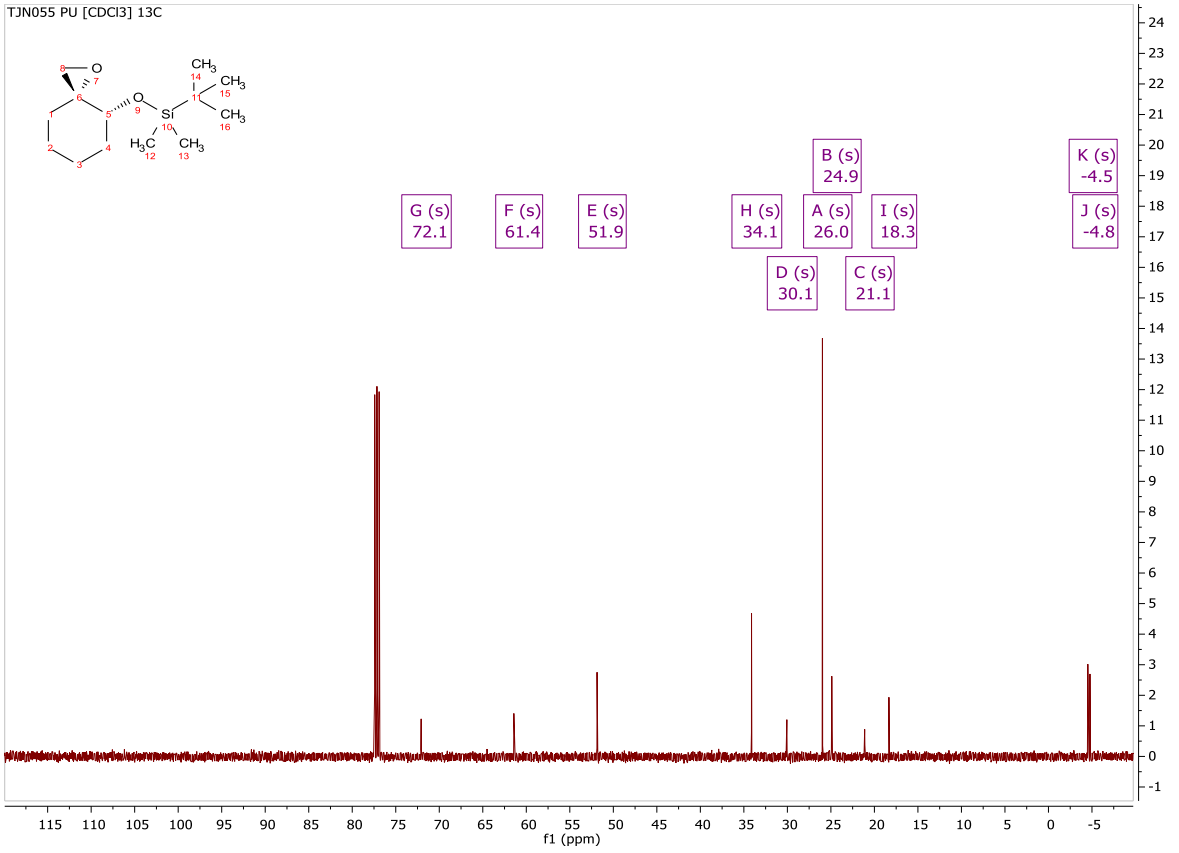


(1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-(hydroxymethyl)cyclohexan-1-ol II-53



(((3*R*,4*R*)-1-Oxaspiro[2.5]octan-4-yl)oxy)(*tert*-butyl)dimethylsilane II-54

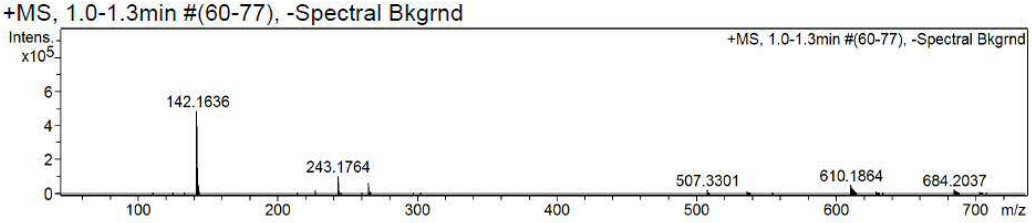




Confirmation of Expected Formula

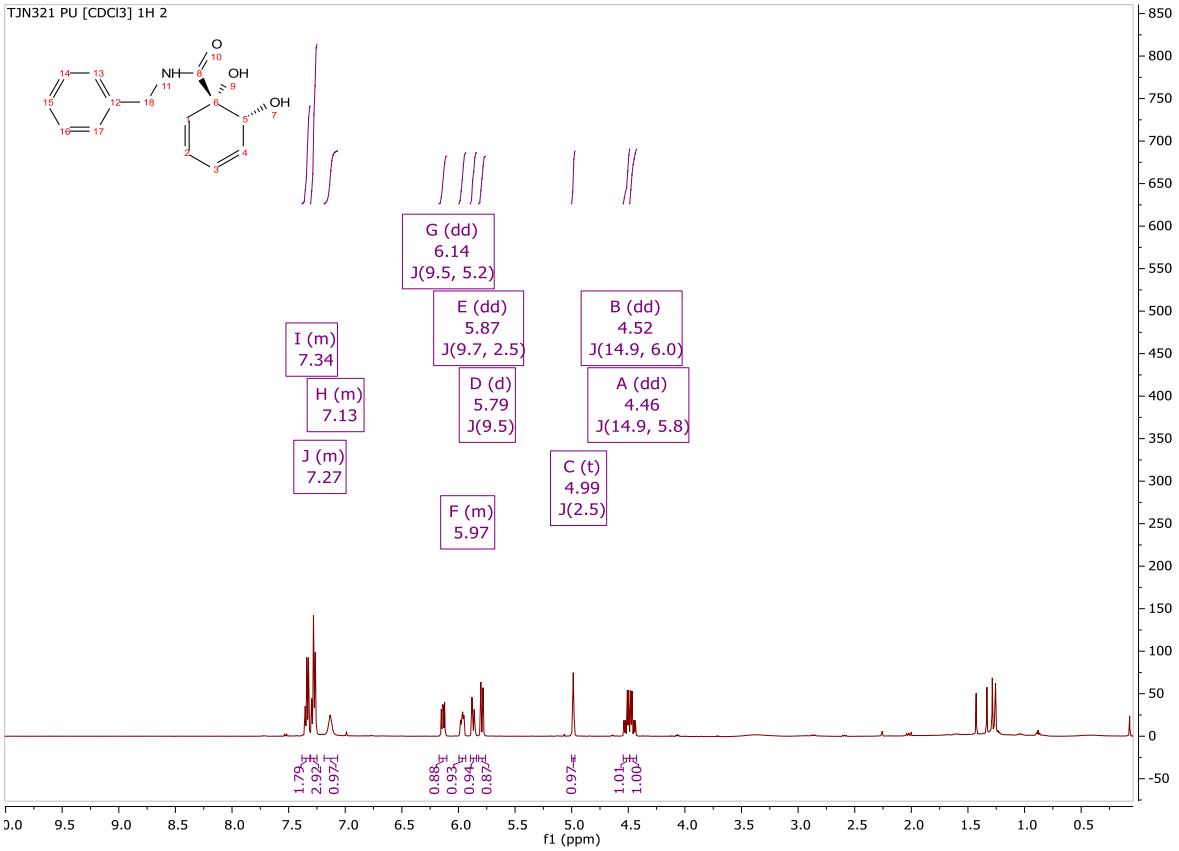
Sample-ID	tn_sel_055	Submitter	Toby Nash
Analysis Name	tn_sel_055_343913_53_01_48332.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	01/06/2015 09:22:21
Ionisation Mode	positive electrospray (ESI)		

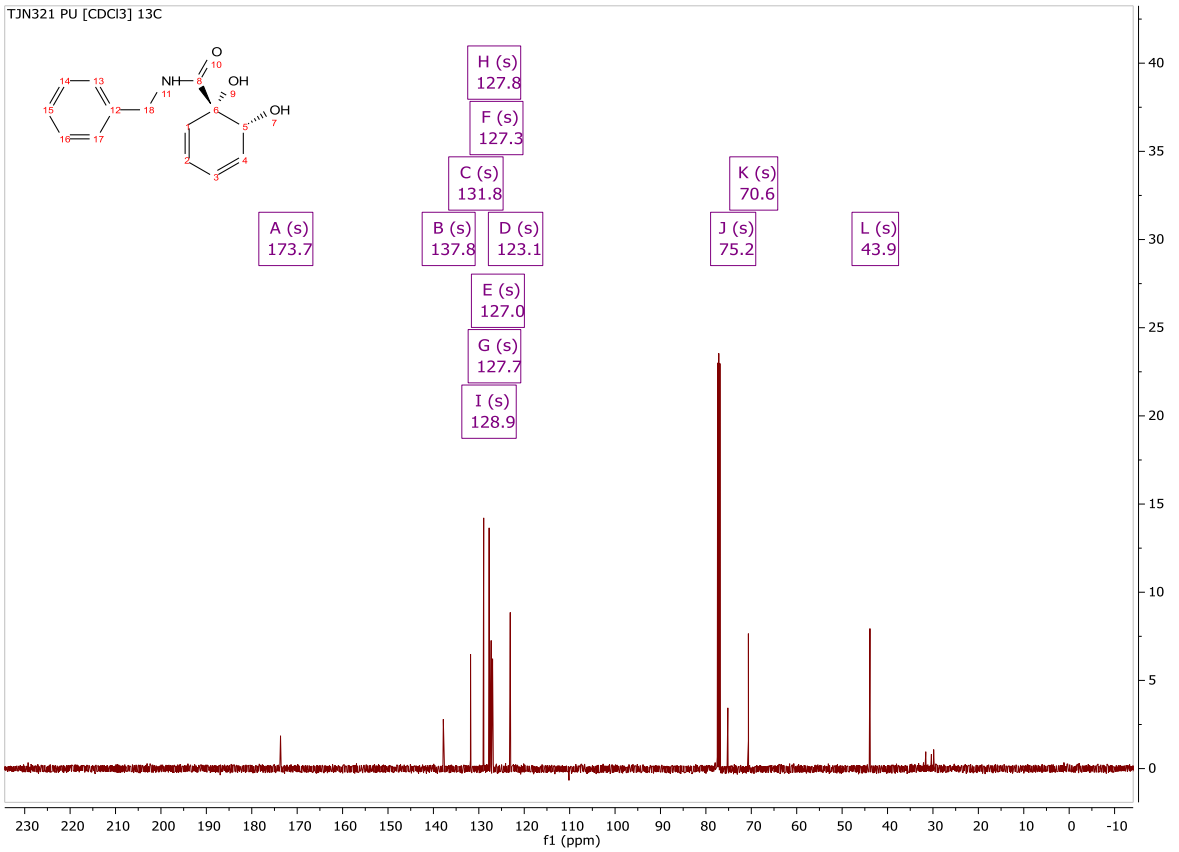
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	142.1636	483119	100.0	10557	34888.3
2	143.1642	51439	10.6	1488	3615.7
3	243.1764	102176	21.1	4719	3677.5
4	244.1781	19392	4.0	1061	684.2
5	265.1582	64828	13.4	3294	2363.0
6	507.3301	24099	5.0	2823	537.5
7	610.1864	49553	10.3	7069	622.7
8	611.1886	29026	6.0	3256	359.8
9	612.1819	26879	5.6	2852	328.8
10	684.2037	24252	5.0	2658	459.7

(1*S*,6*R*)-*N*-benzyl-1,6-dihydroxycyclohexa-2,4-diene-1-carboxamide II-55

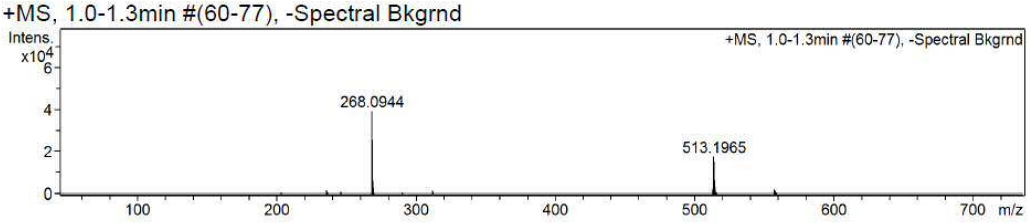




Confirmation of Expected Formula

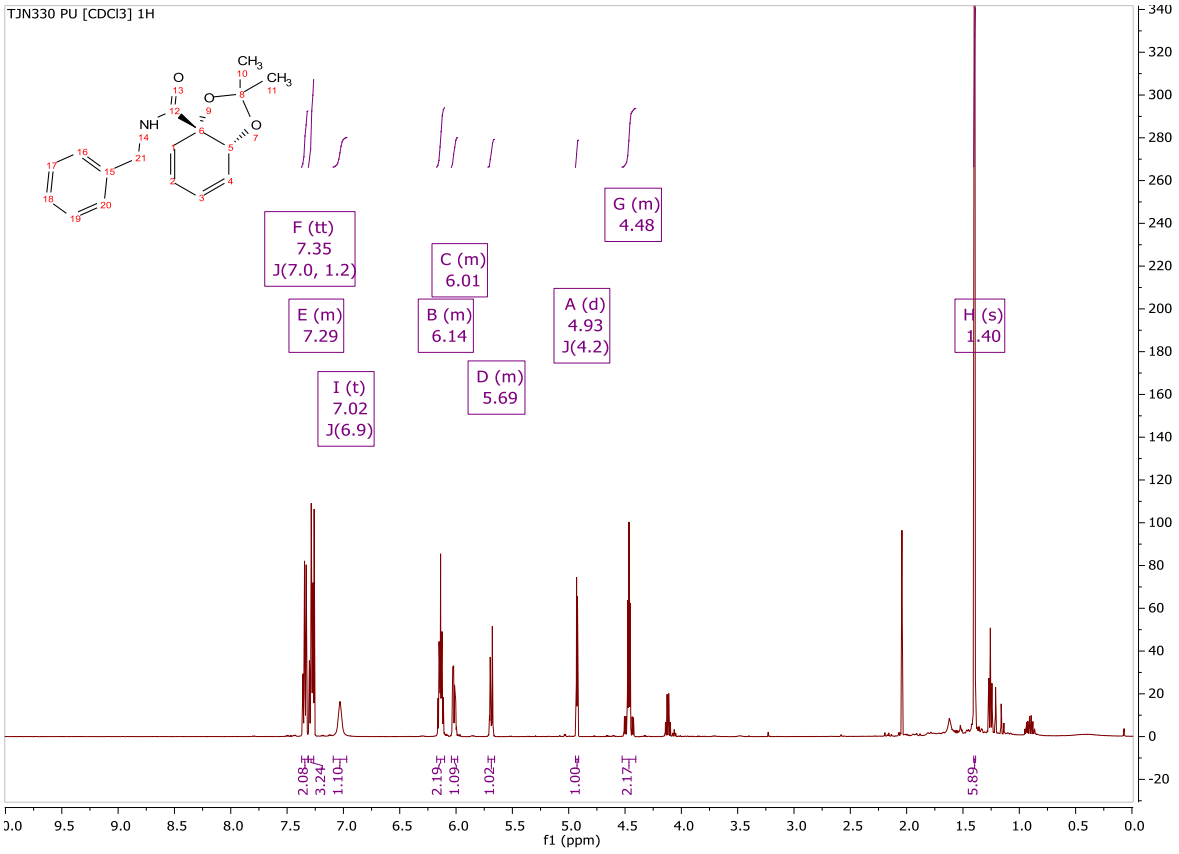
Sample-ID	tn_sel_TJN321	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN321_351459_30_01_56852.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	23/03/2017 16:17:13
Ionisation Mode	positive electrospray (ESI)		

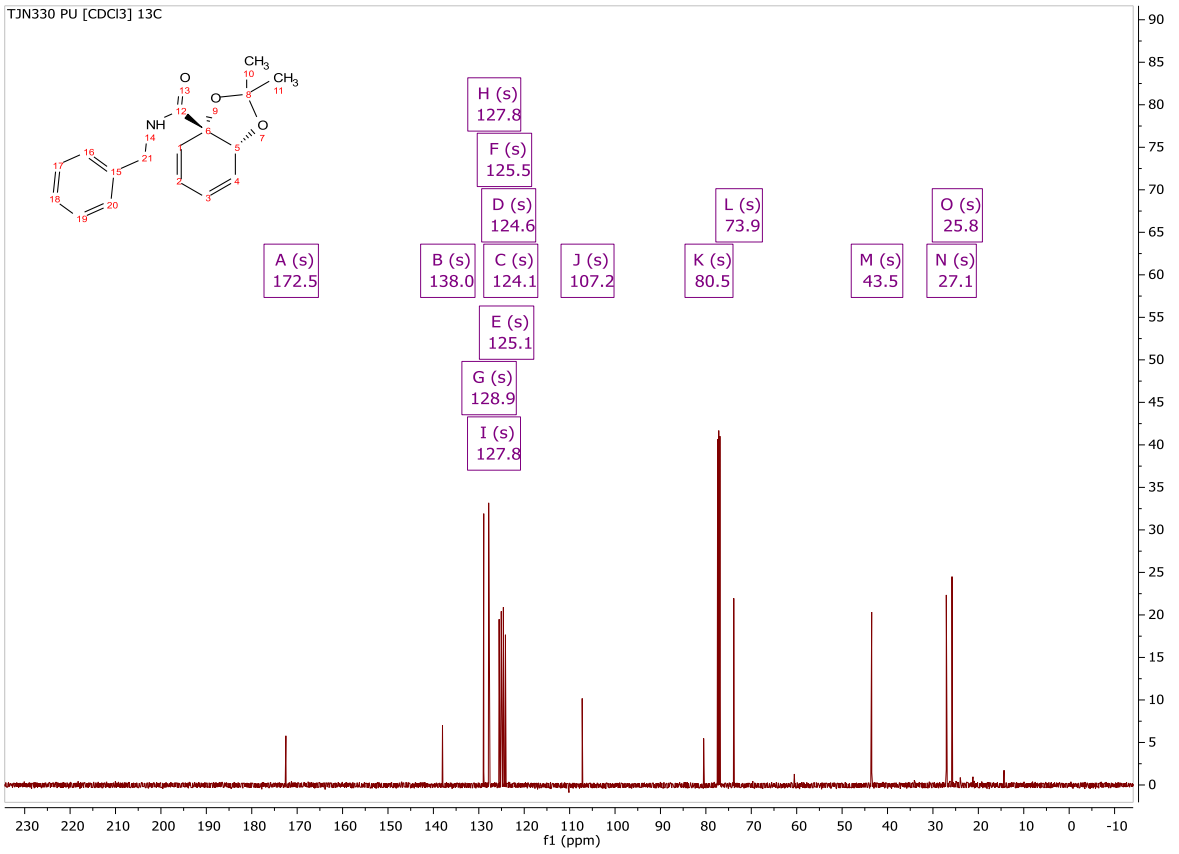
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

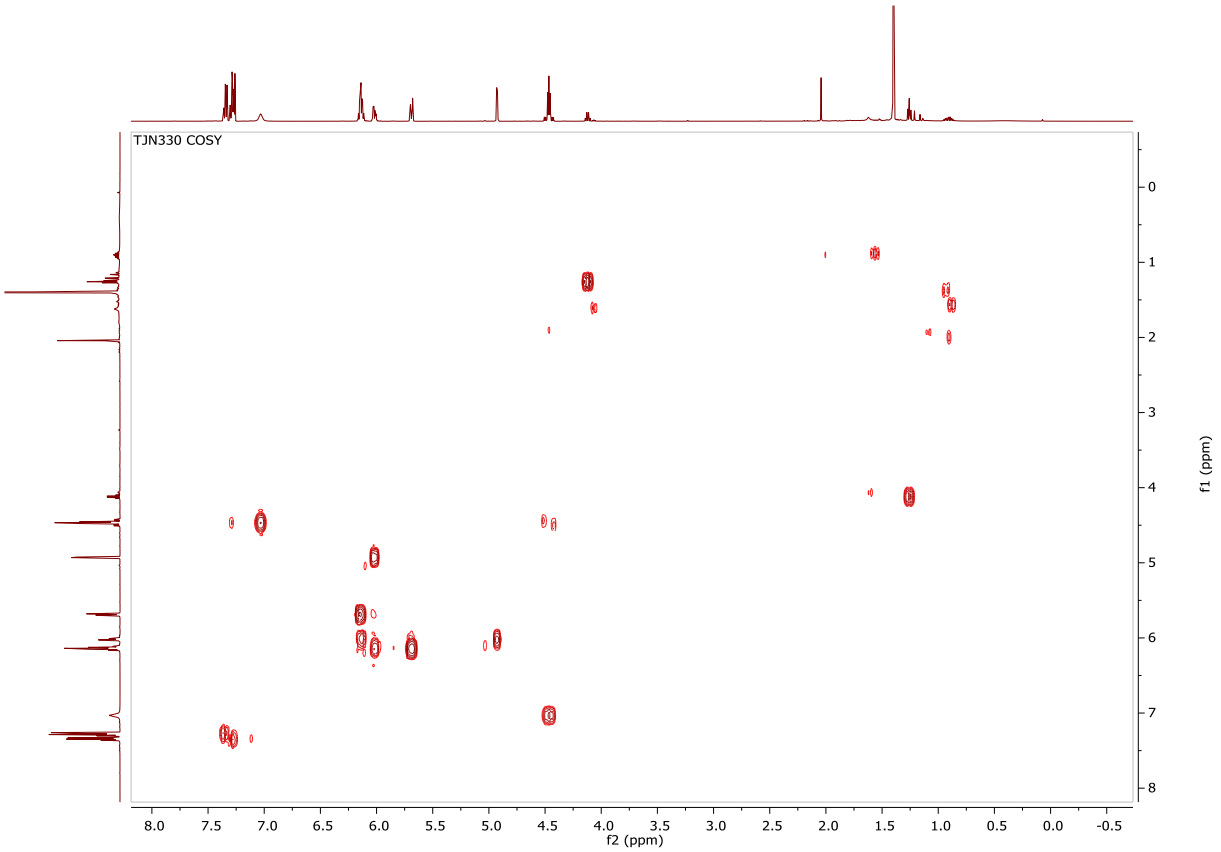


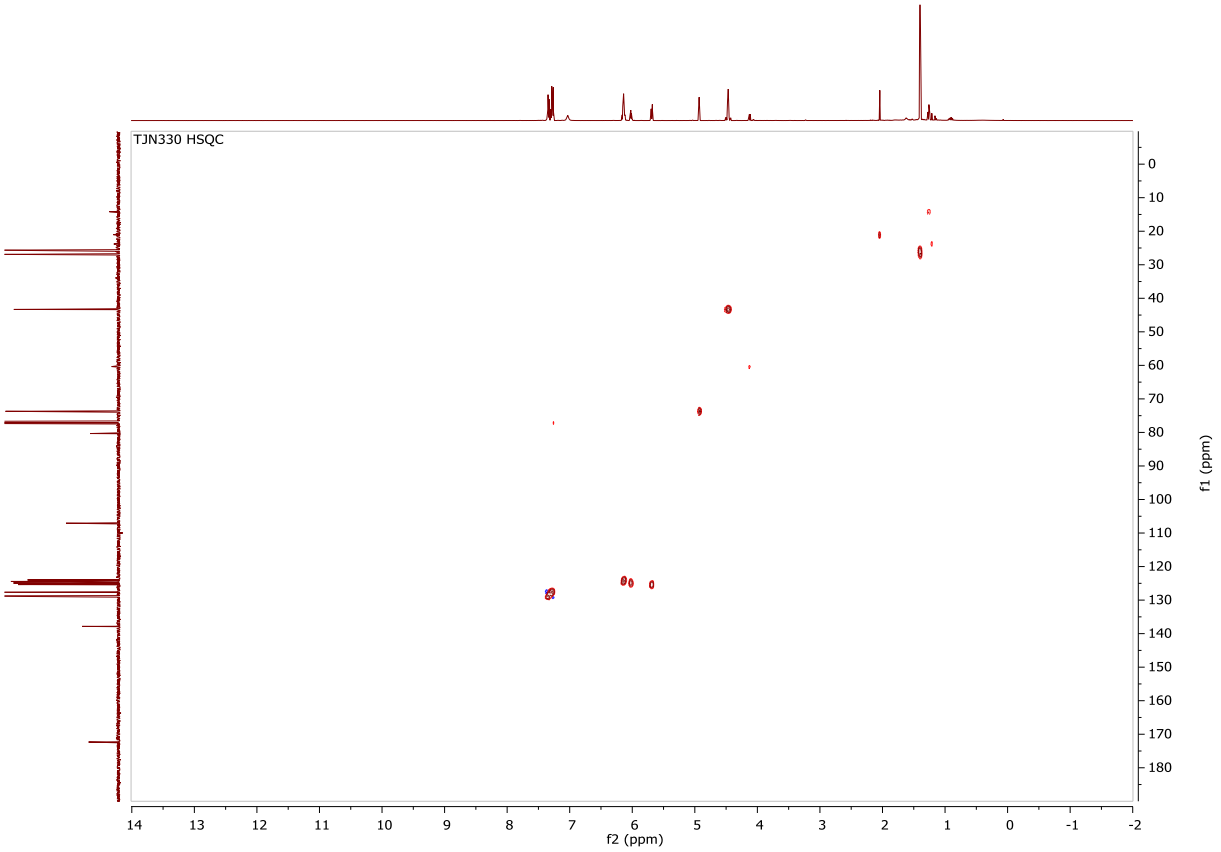
#	m/z	I	I %	Area	S/N
1	203.0570	769	2.0	23	840.2
2	236.0779	1526	3.9	72	606.6
3	246.1150	807	2.1	47	265.4
4	268.0944	39042	100.0	1660	14602.4
5	269.0978	4130	10.6	201	1569.1
6	290.1322	591	1.5	33	336.0
7	312.1127	1537	3.9	90	1077.6
8	513.1965	17479	44.8	1597	4342.1
9	514.2024	3631	9.3	366	890.4
10	557.2157	1783	4.6	214	434.0

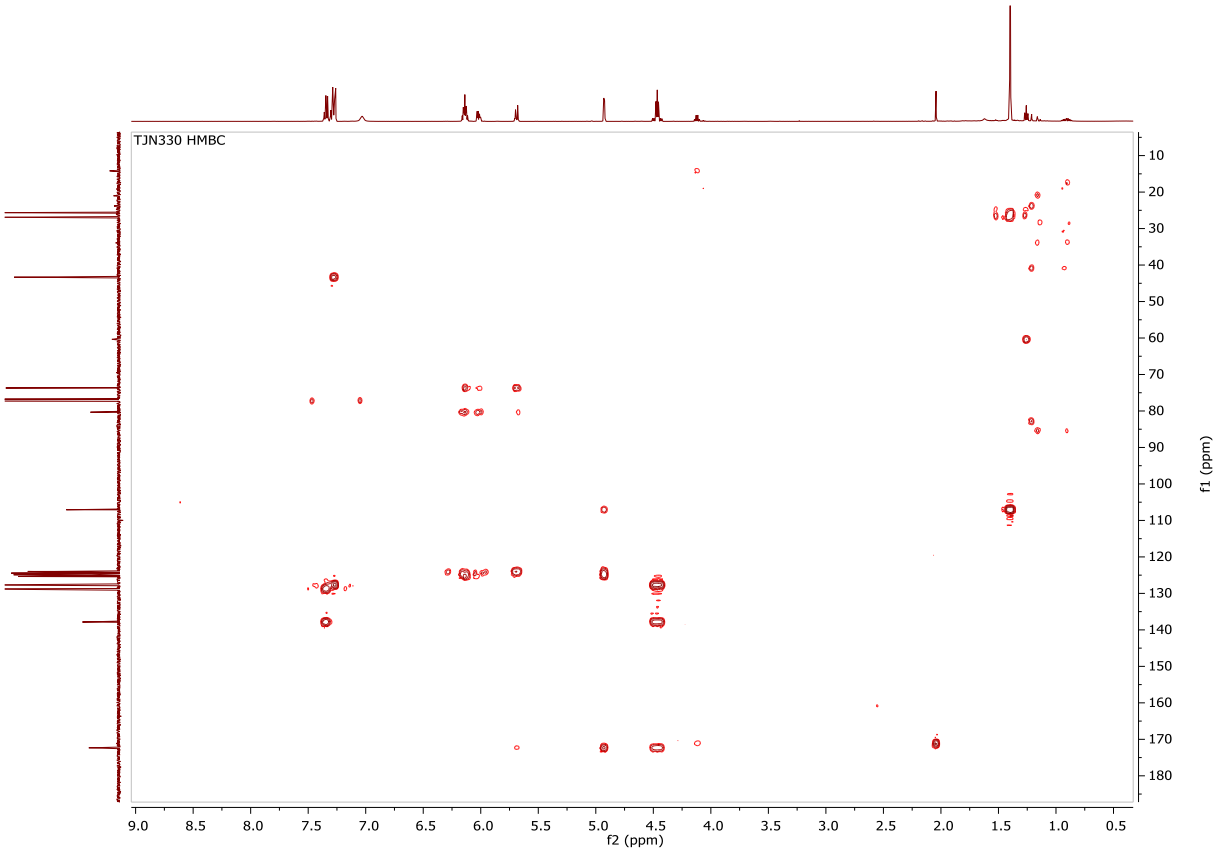
(3a*S*,7a*R*)-*N*-benzyl-2,2-dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxamide II-57






TJN330 COSY
f2 (ppm)
f1 (ppm)

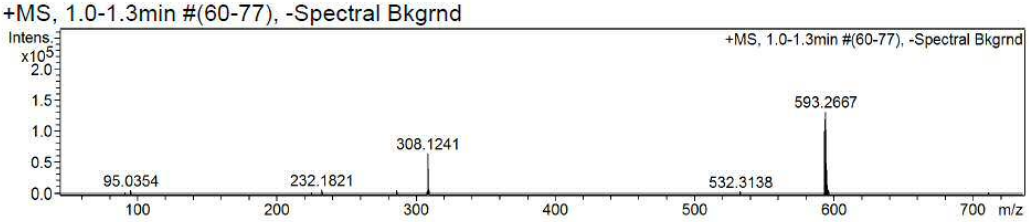

TJN330 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

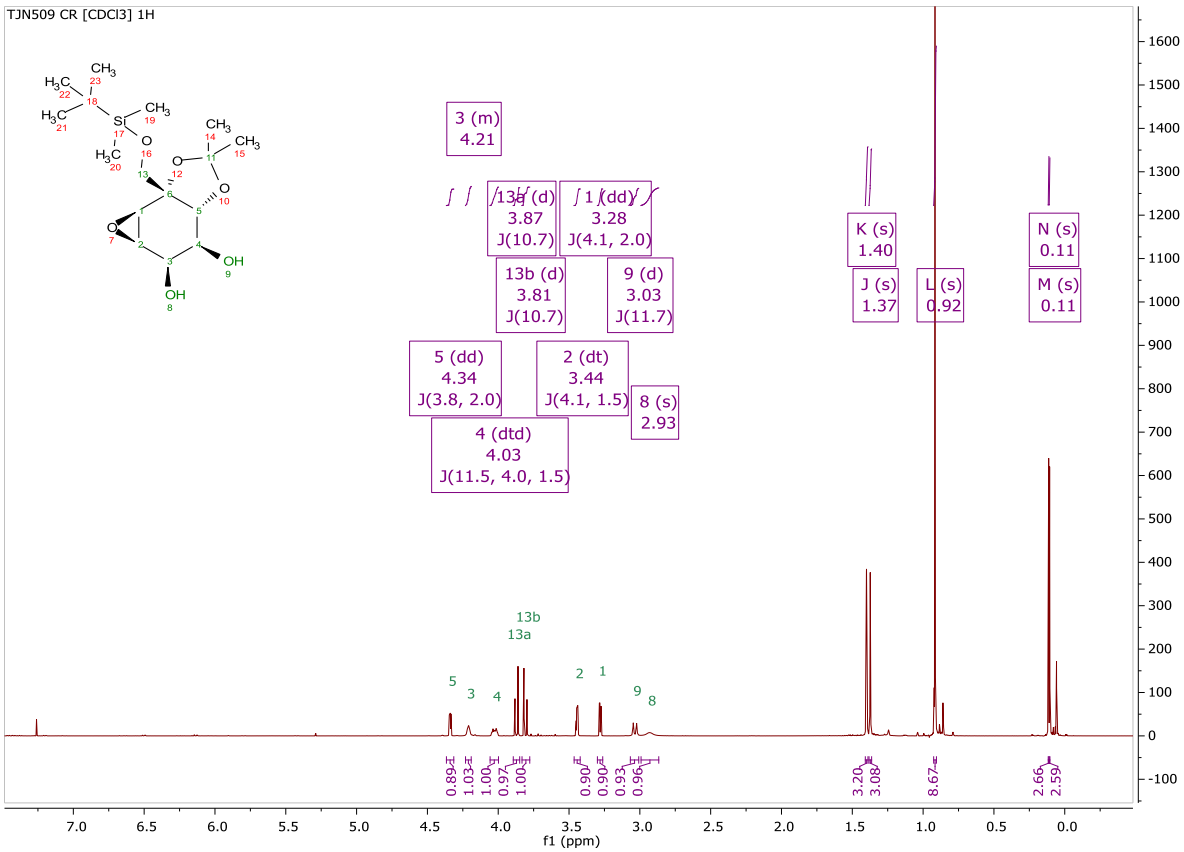
Sample-ID	tn_sel_TJN330	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN330_351460_31_01_56853.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	23/03/2017 16:20:43
Ionisation Mode	positive electrospray (ESI)		

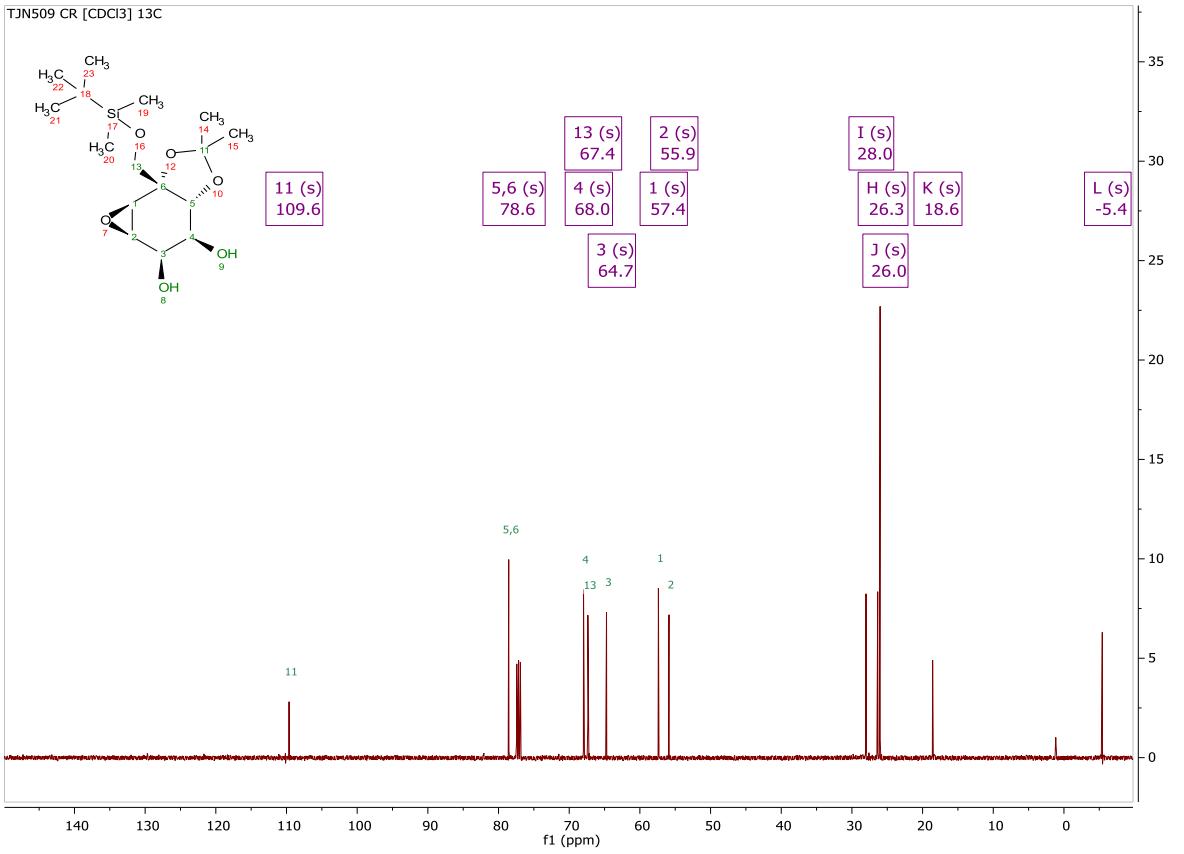
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

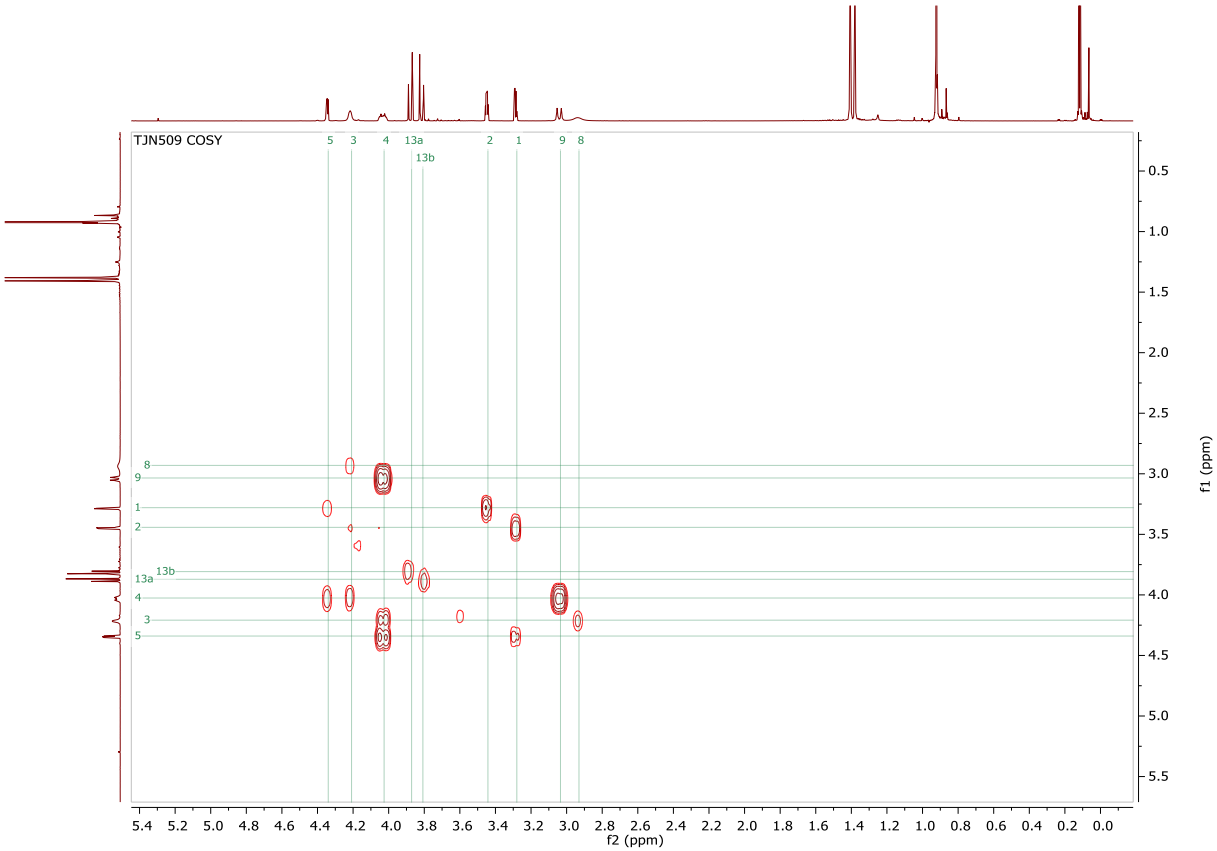


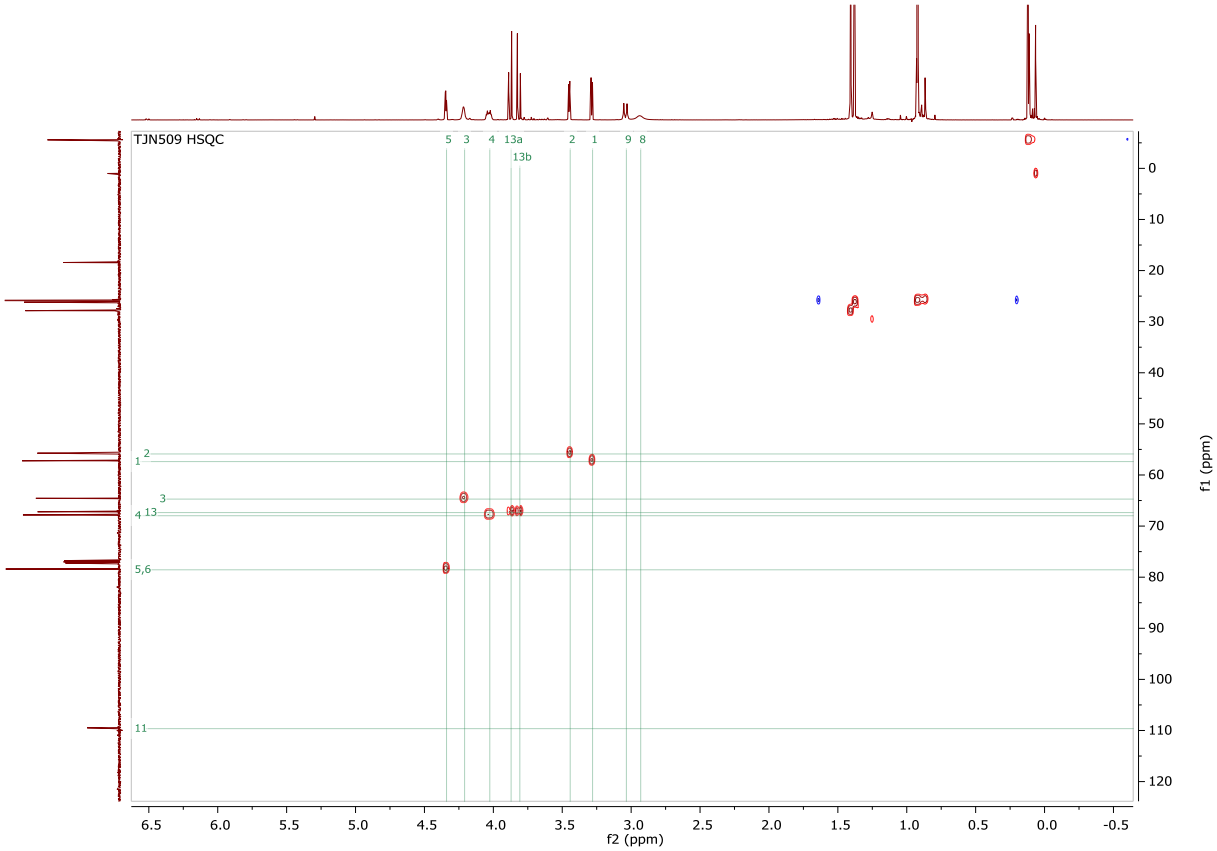
#	m/z	I	I %	Area	S/N
1	91.0393	2324	1.8	25	5318.7
2	95.0354	5137	3.9	86	11254.0
3	232.1821	6174	4.7	277	4505.4
4	286.1442	4515	3.4	261	1206.7
5	308.1241	64416	49.1	3203	17371.4
6	309.1296	7816	6.0	442	2151.1
7	532.3138	3506	2.7	408	644.2
8	593.2667	131202	100.0	11047	11512.9
9	594.2645	49598	37.8	4986	4477.2
10	595.2685	6083	4.6	670	565.4

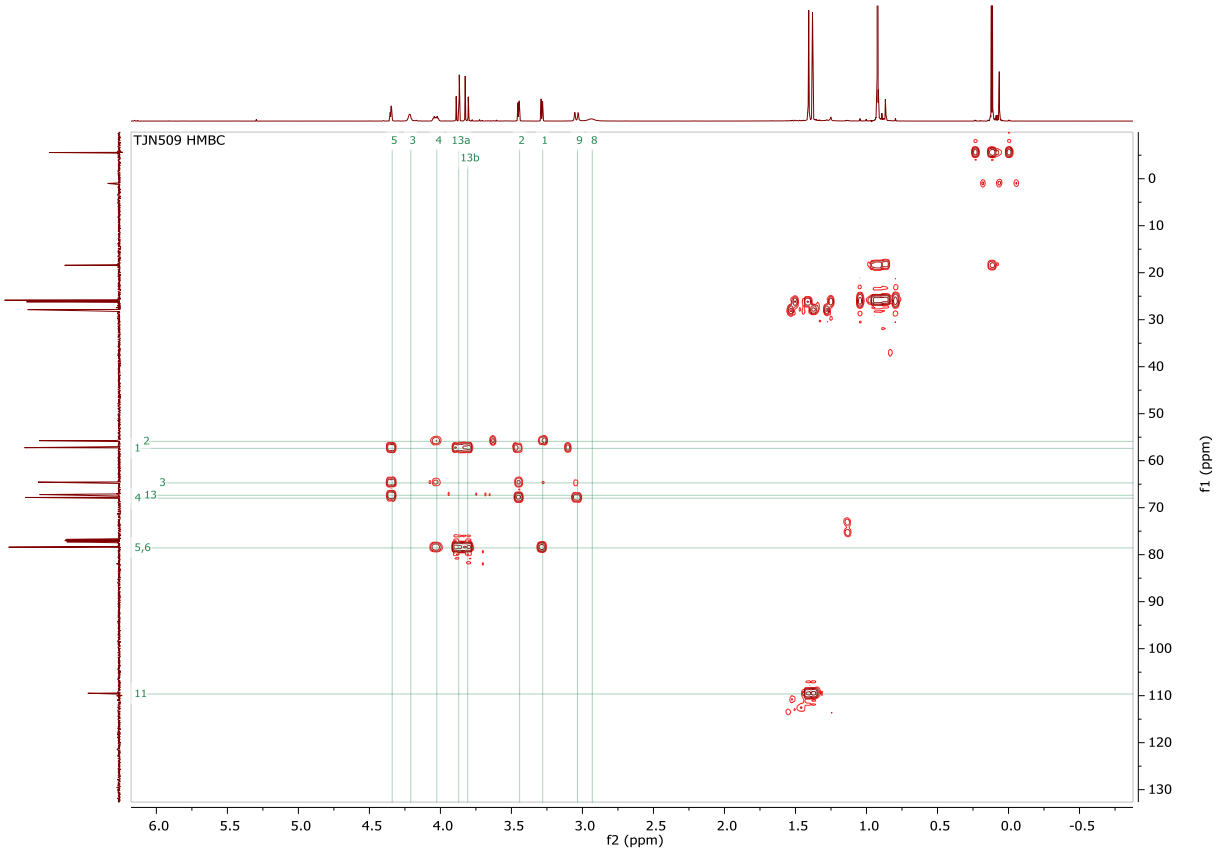
(3a*R*,4*S*,5*R*,5a*R*,6a*R*,6b*S*)-6b-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethylhexahydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxole-4,5-diol II-59






TJN509 COSY
5 3 4 13a 13b 2 1 9 8
f2 (ppm)
f1 (ppm)

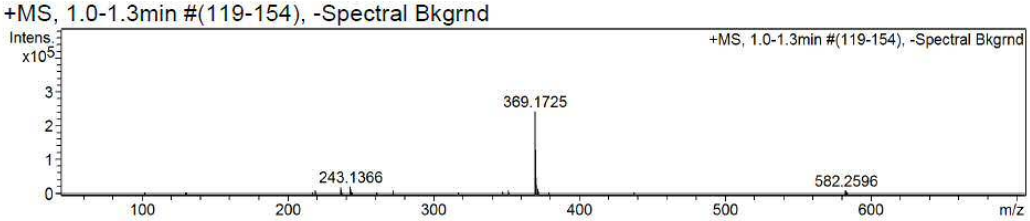

TJN509 HSQC
5 3 4 13a 13b 2 1 9 8
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

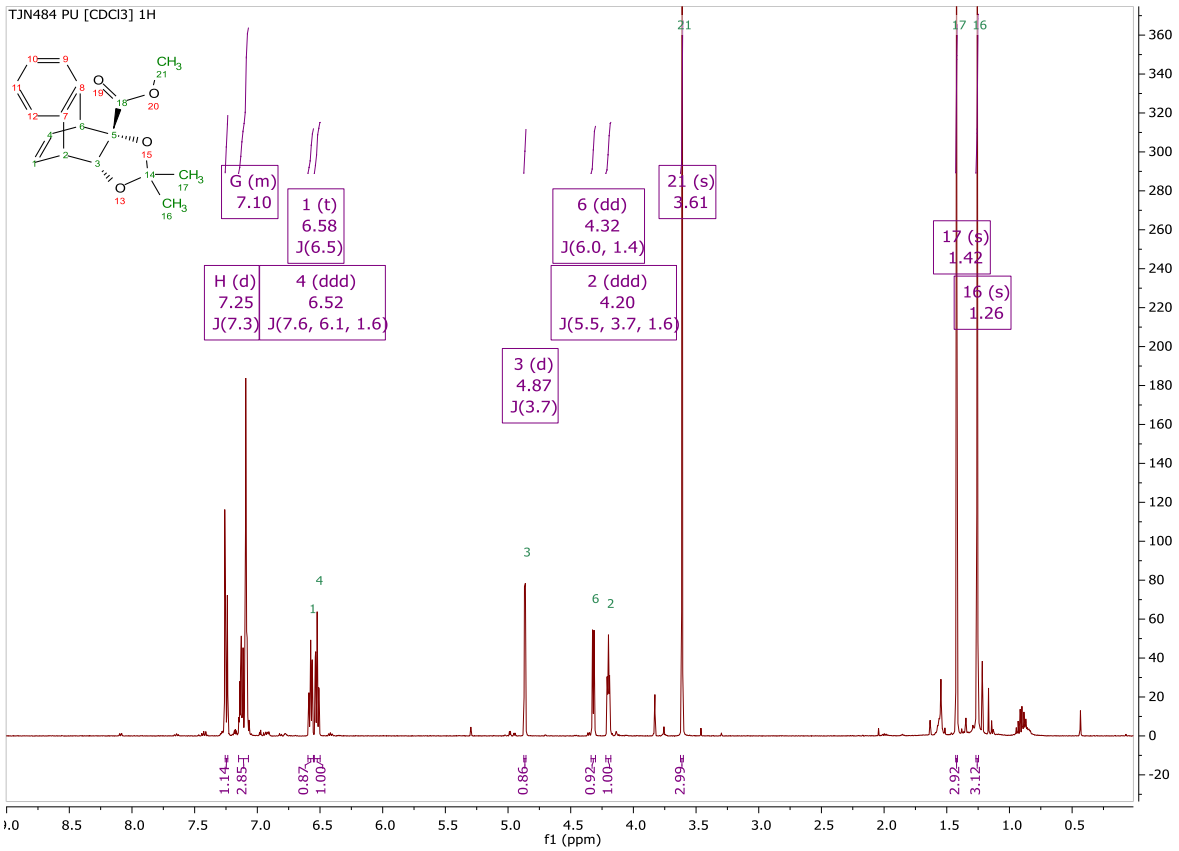
Sample-ID	tn_sel_TJN509	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN509_357165_38_01_63355.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	15/05/2018 13:50:36
Ionisation Mode	positive electrospray (ESI)		

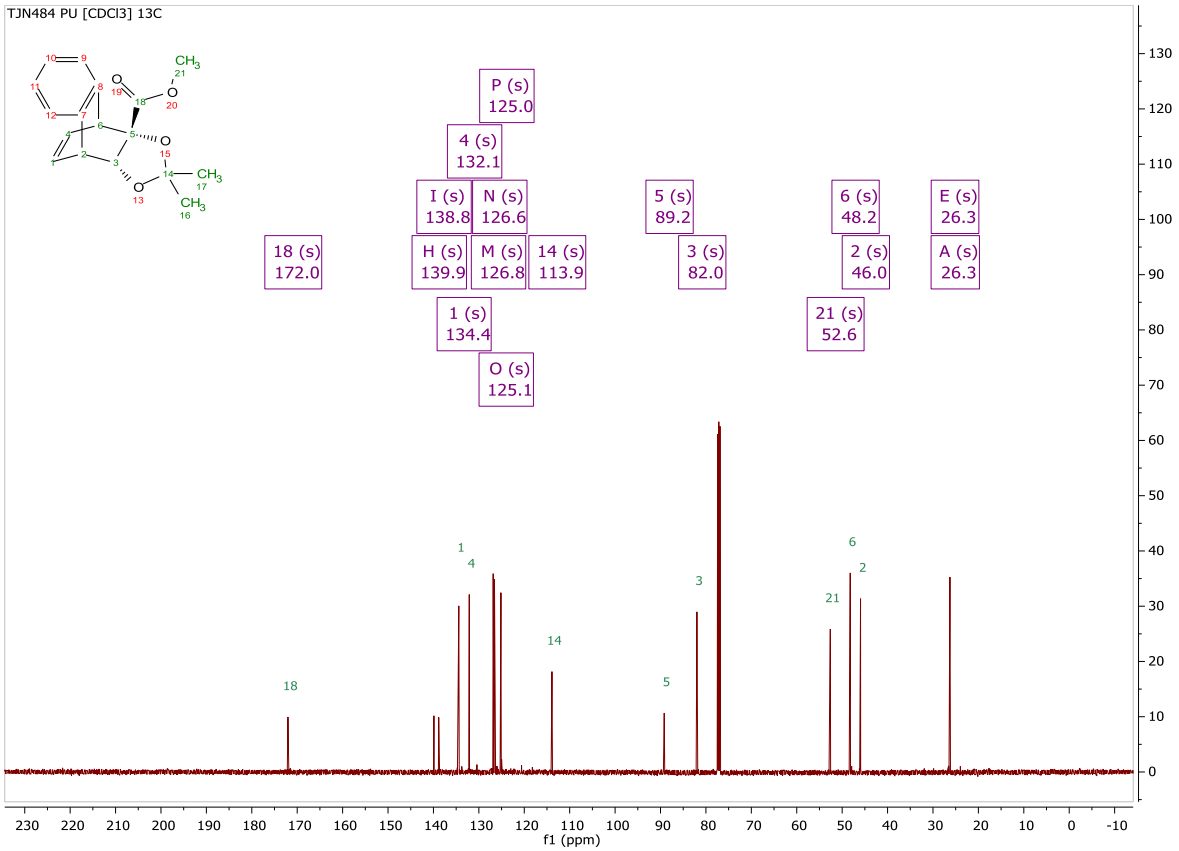
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

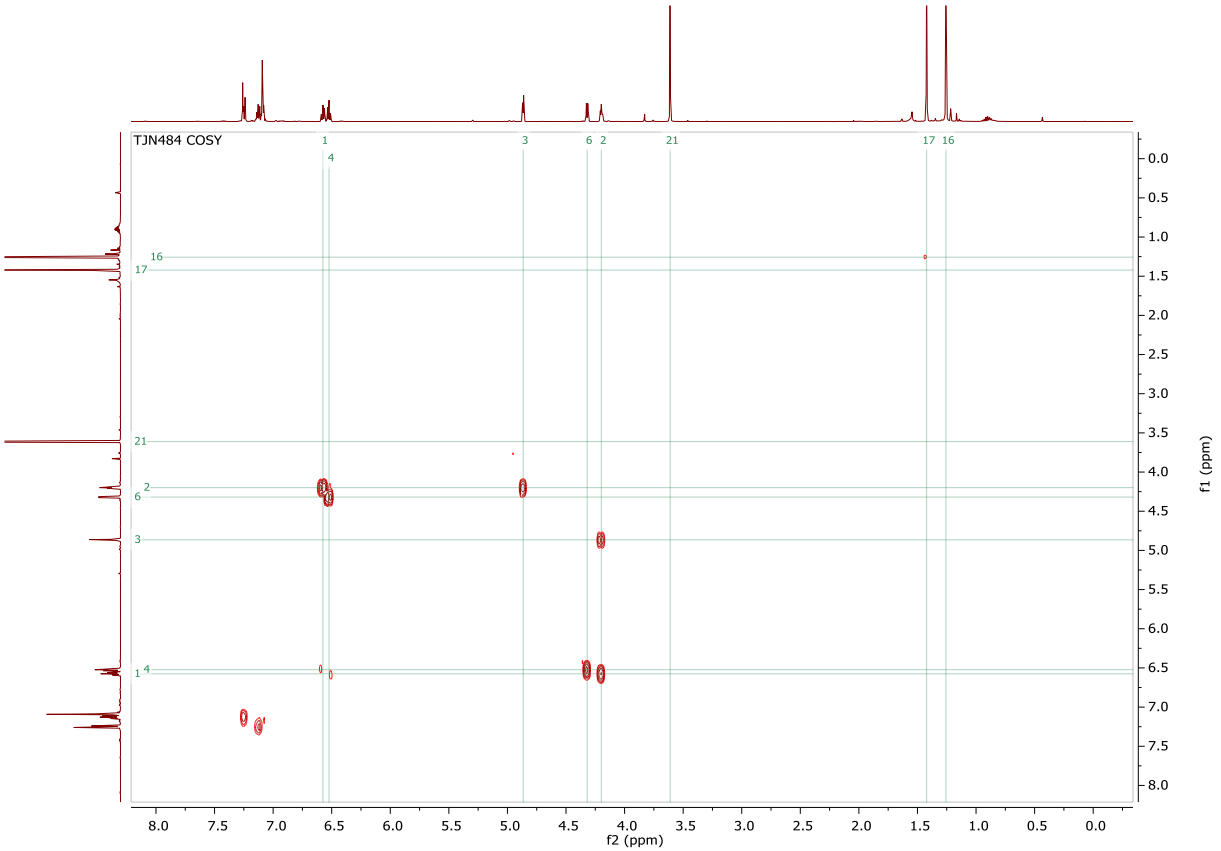


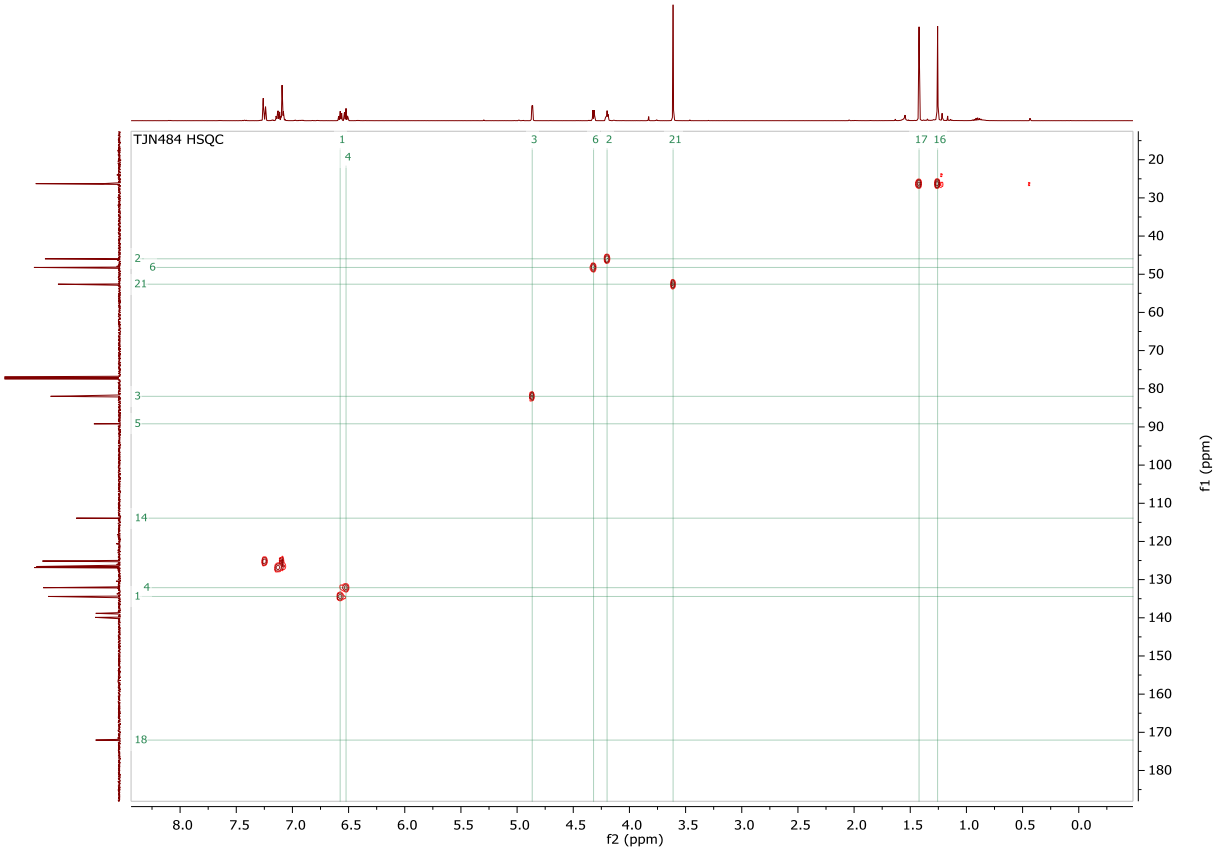
#	m/z	I	I %	Area	S/N
1	219.1370	10327	4.3	328	916.7
2	236.0945	16960	7.0	212	1070.8
3	243.1366	21493	8.9	915	1215.4
4	272.2029	8739	3.6	115	451.4
5	347.1990	6263	2.6	406	162.1
6	351.1619	8525	3.5	484	205.9
7	369.1725	241446	100.0	15692	4467.0
8	370.1753	49082	20.3	3078	896.3
9	371.1738	13695	5.7	765	246.9
10	582.2596	10514	4.4	1003	674.9

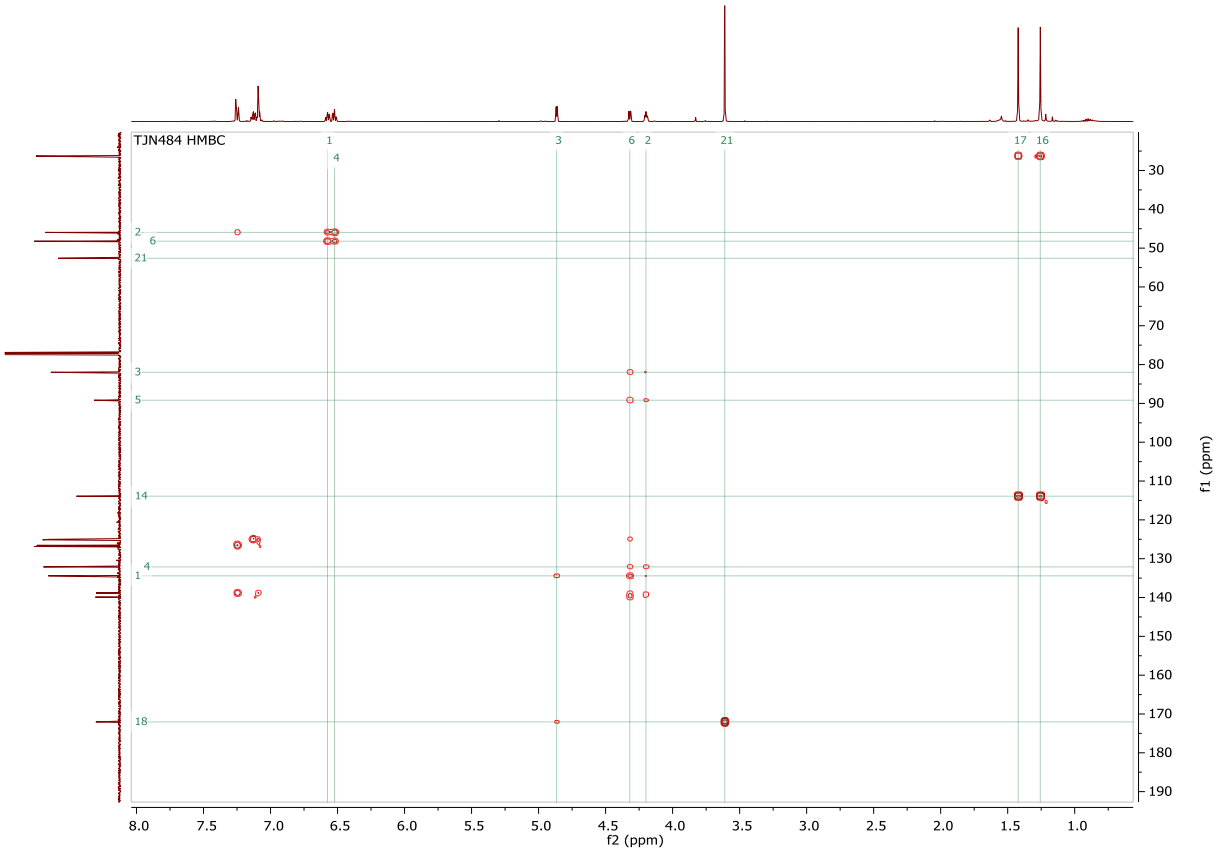
Methyl (3a*S*,4*S*,9*R*,9a*R*)-2,2-dimethyl-9,9a-dihydro-4,9-ethenonaphtho[2,3-d][1,3]dioxole-3a(4H)-carboxylate II-61






TJN484 COSY
f2 (ppm)
f1 (ppm)

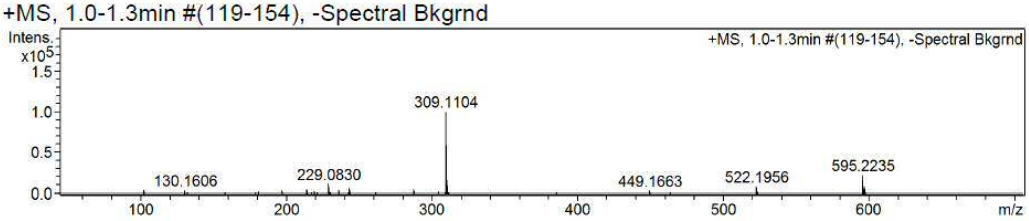

TJN484 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

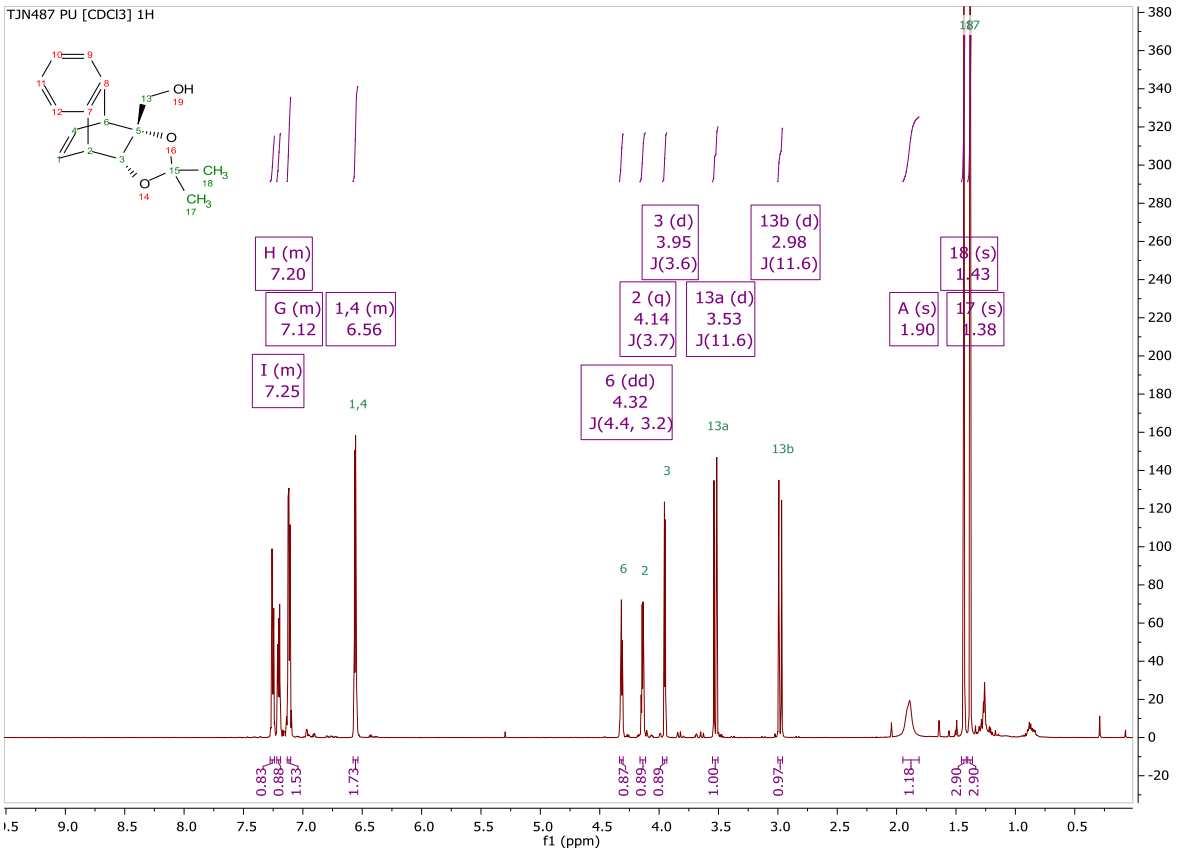
Sample-ID	tn_sel_TJN484	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN484_356395_82_01_62468.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	22/03/2018 16:25:15
Ionisation Mode	positive electrospray (ESI)		

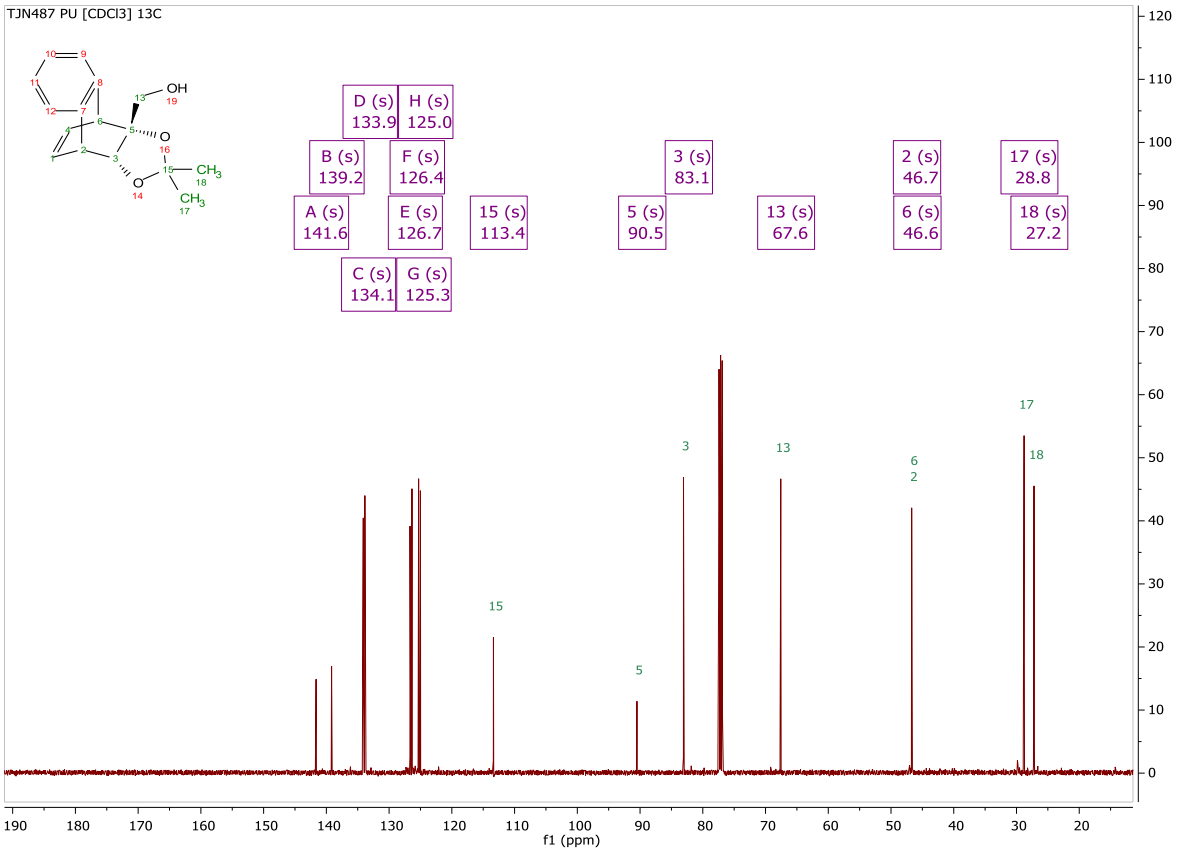
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

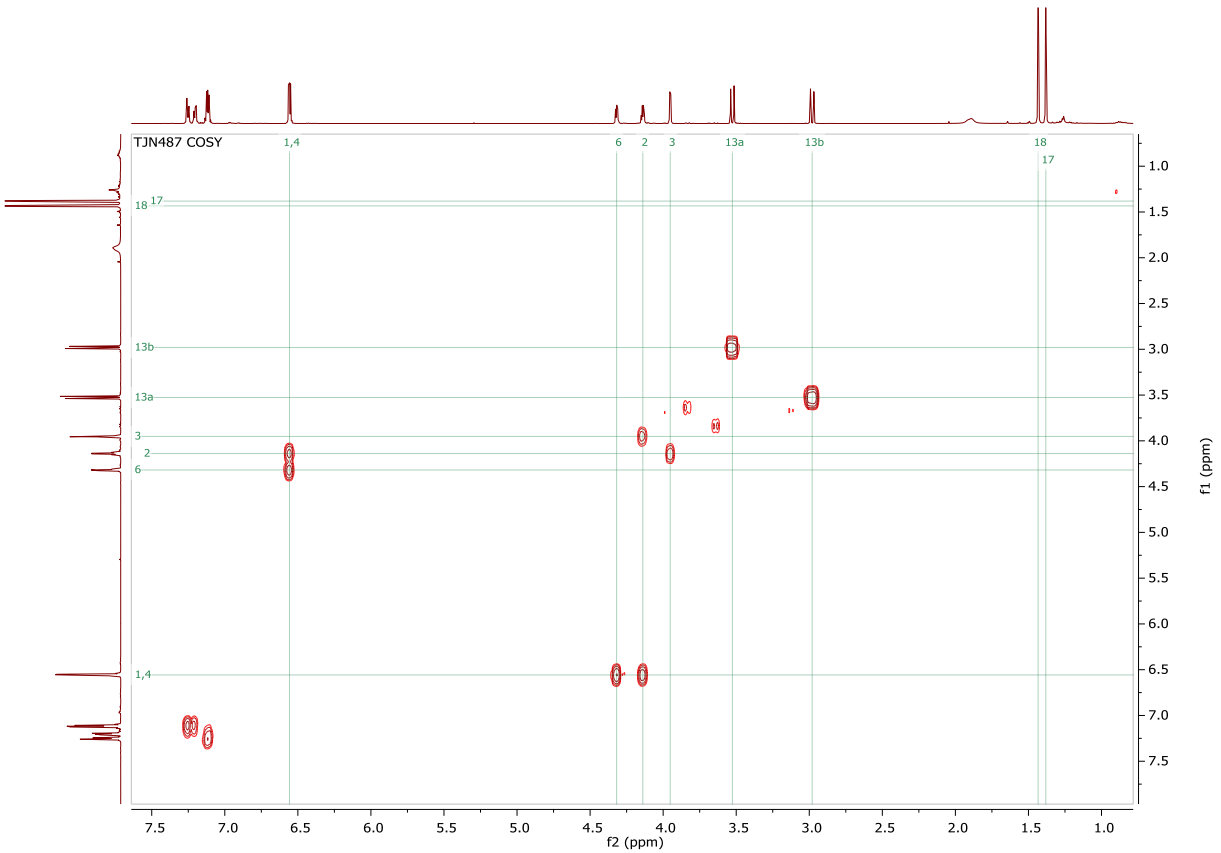


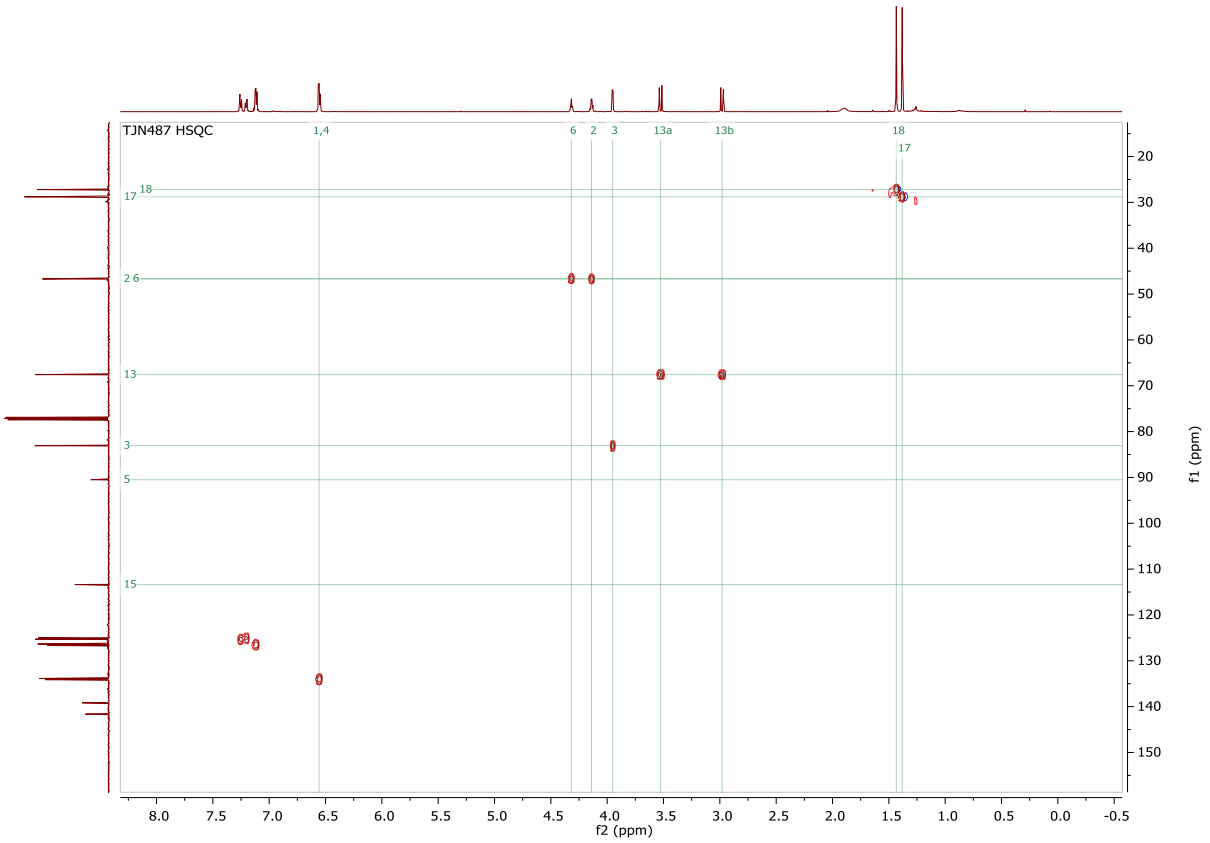
#	m/z	I	I %	Area	S/N
1	214.0937	5218	5.2	157	716.7
2	229.0830	11534	11.5	418	1261.1
3	236.0765	4047	4.0	96	404.1
4	243.1358	6727	6.7	314	618.1
5	287.1253	4808	4.8	223	409.1
6	309.1104	100188	100.0	5541	6486.6
7	310.1137	16479	16.4	844	1055.4
8	522.1956	8855	8.8	774	1212.1
9	595.2235	22937	22.9	2292	2027.0
10	596.2271	8343	8.3	853	750.0

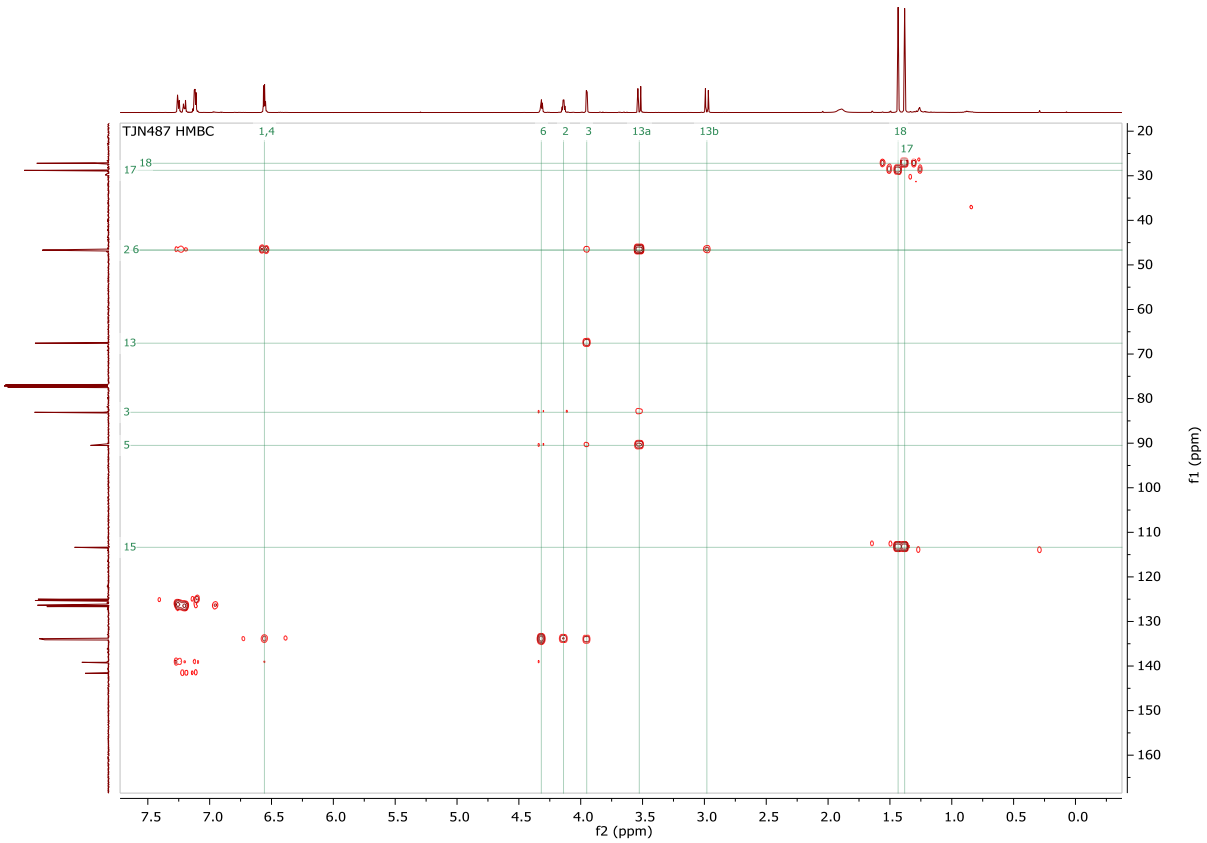
((3a*R*,4*S*,9*R*,9a*R*)-2,2-Dimethyl-9,9a-dihydro-4,9-ethenonaphtho[2,3-d][1,3]dioxol-3a(4H)-yl)methanol II-62






TJN487 COSY
1,4
6
2
3
13a
13b
18
17
f2 (ppm)
f1 (ppm)

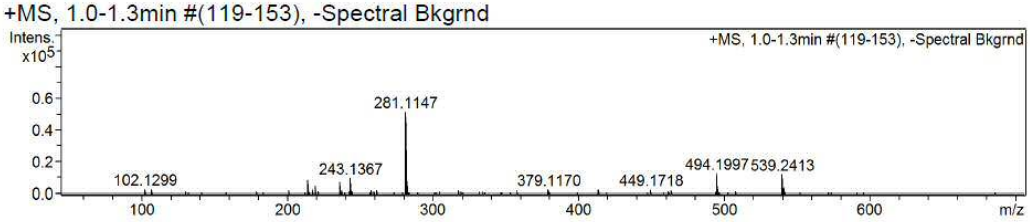

TJN487 HSQC
1,4
6
2
3
13a
13b
18
17
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

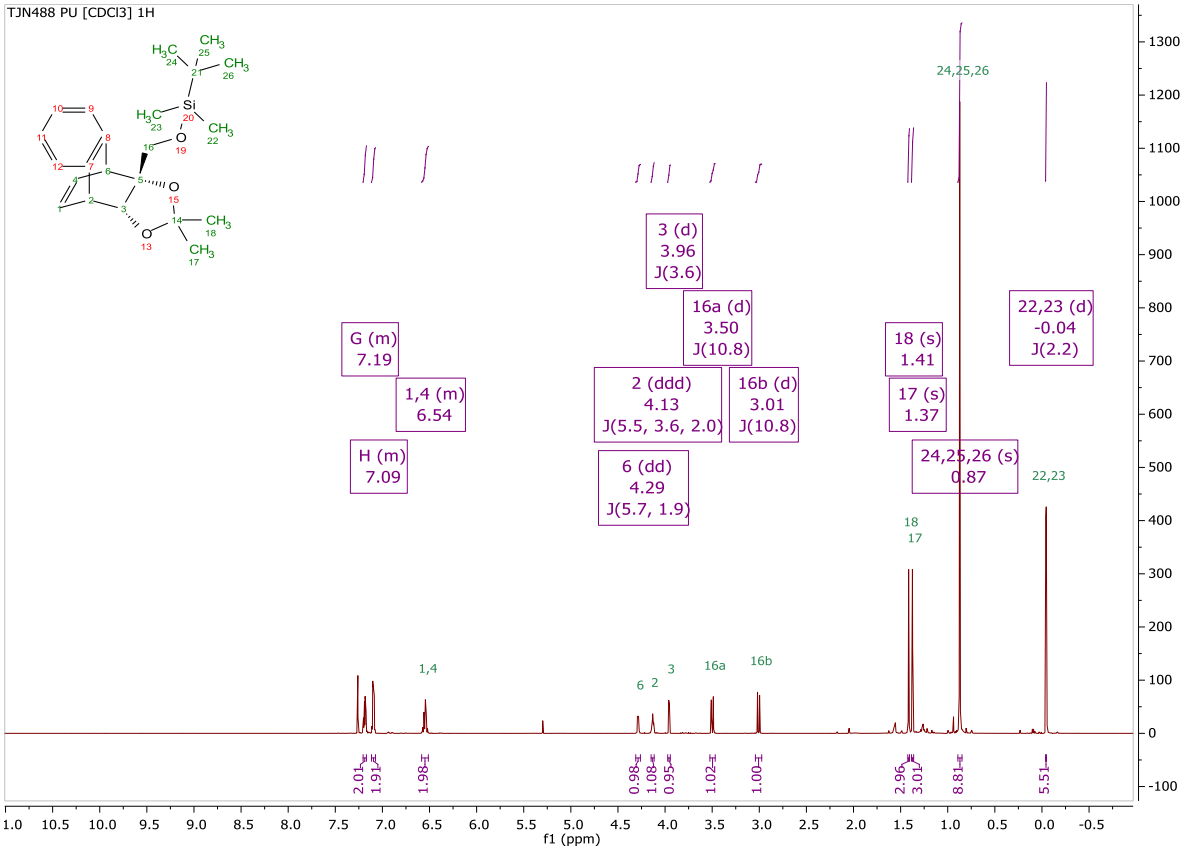
Sample-ID	tn_sel_TJN487	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN487_356505_92_01_62591.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	27/03/2018 11:43:01
Ionisation Mode	positive electrospray (ESI)		

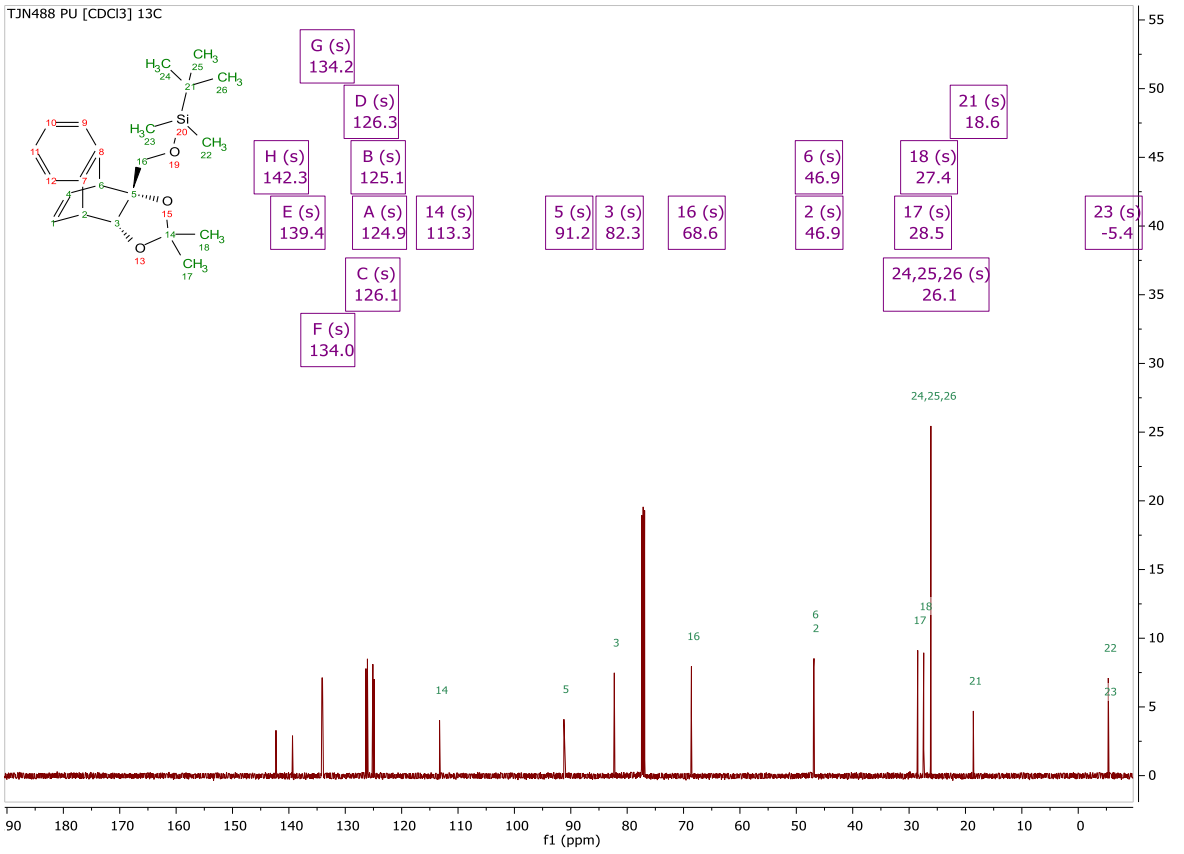
+MS, 1.0-1.3min #(119-153), -Spectral Bkgrnd

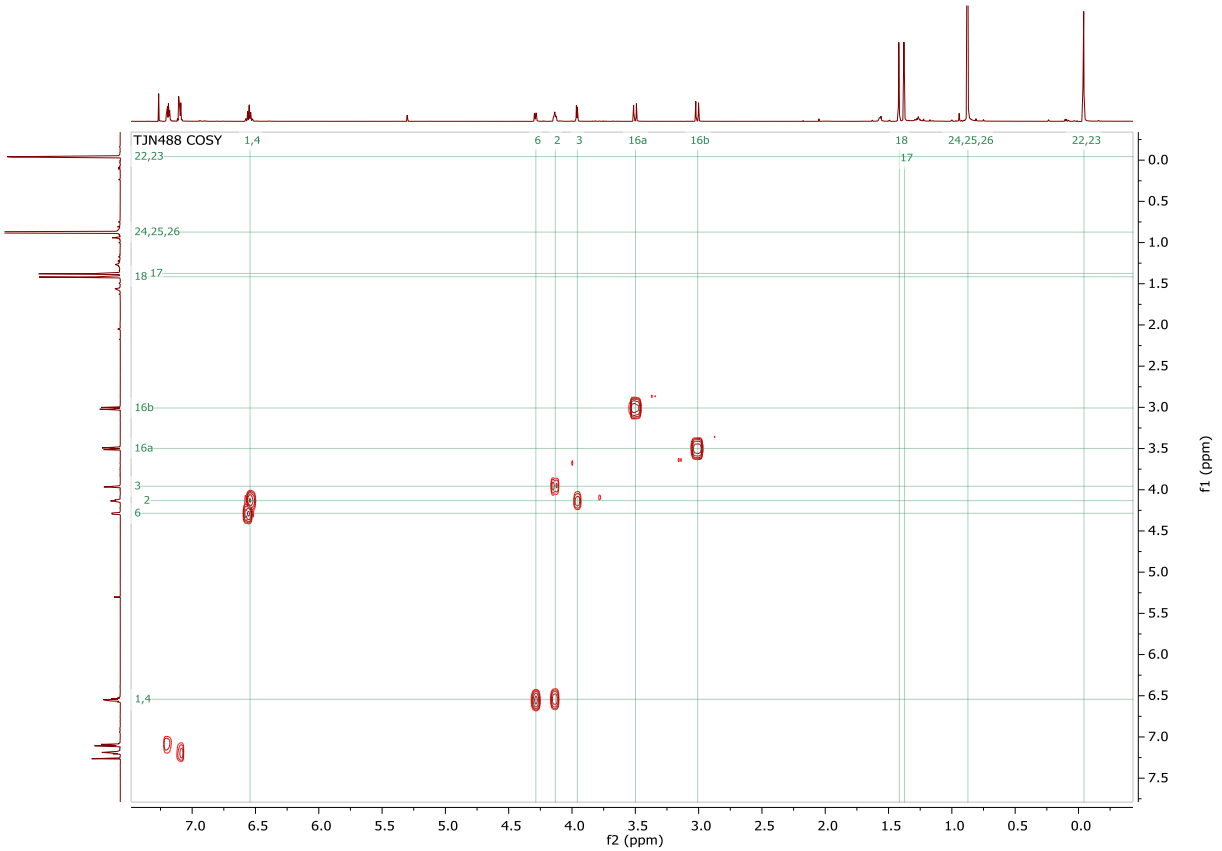


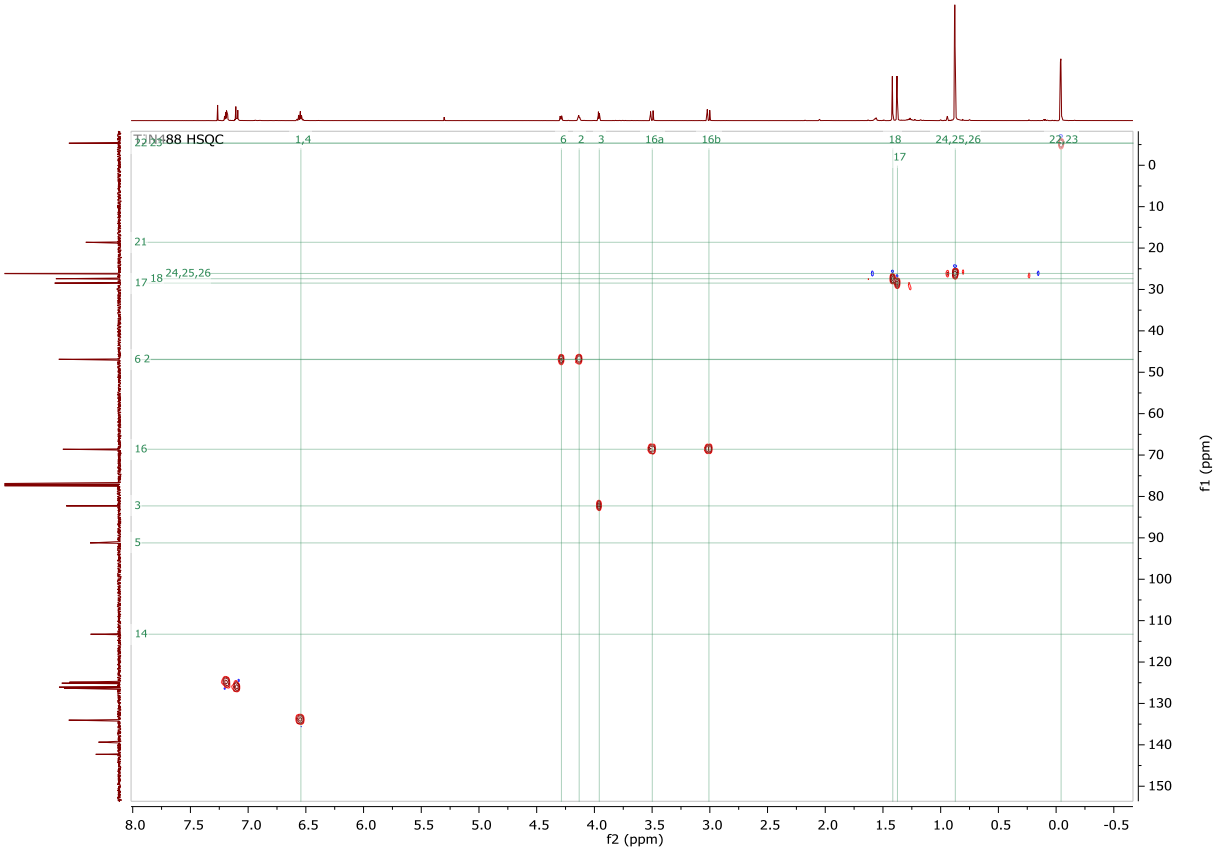
#	m/z	I	I %	Area	S/N
1	214.0943	8798	17.2	219	928.2
2	219.1360	4914	9.6	187	475.2
3	236.0987	7233	14.1	100	546.4
4	243.1367	9740	19.0	461	674.6
5	281.1147	51271	100.0	2717	2375.6
6	282.1201	7893	15.4	385	362.4
7	494.1997	12442	24.3	1098	760.9
8	495.2048	3764	7.3	315	230.1
9	539.2413	12054	23.5	1257	657.7
10	540.2455	4070	7.9	433	221.2

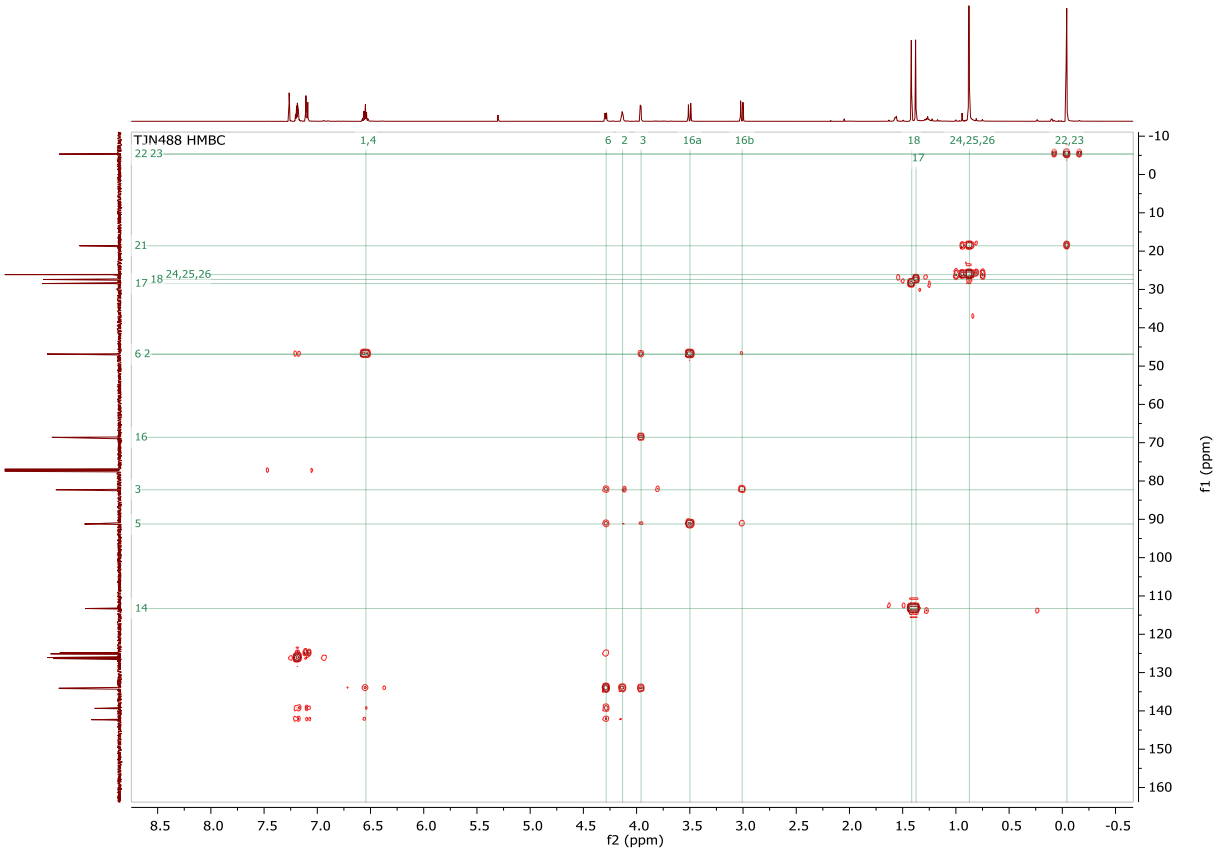
tert-Butyl(((3a*R*,4*S*,9*R*,9a*R*)-2,2-dimethyl-9,9a-dihydro-4,9-ethenonaphtho[2,3-d][1,3]dioxol-3a(4H)-yl)methoxy)dimethylsilane II-63






TJN488 COSY
1,4
6
2
3
16a
16b
18
24,25,26
22,23
17
f2 (ppm)
f1 (ppm)

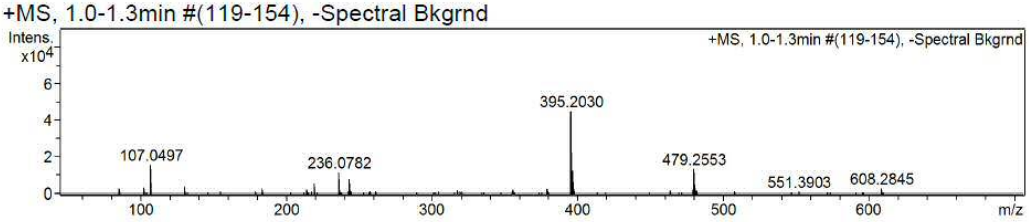

TJN488 HSQC
1,4
6
2
3
16a
16b
18
24,25,26
17
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

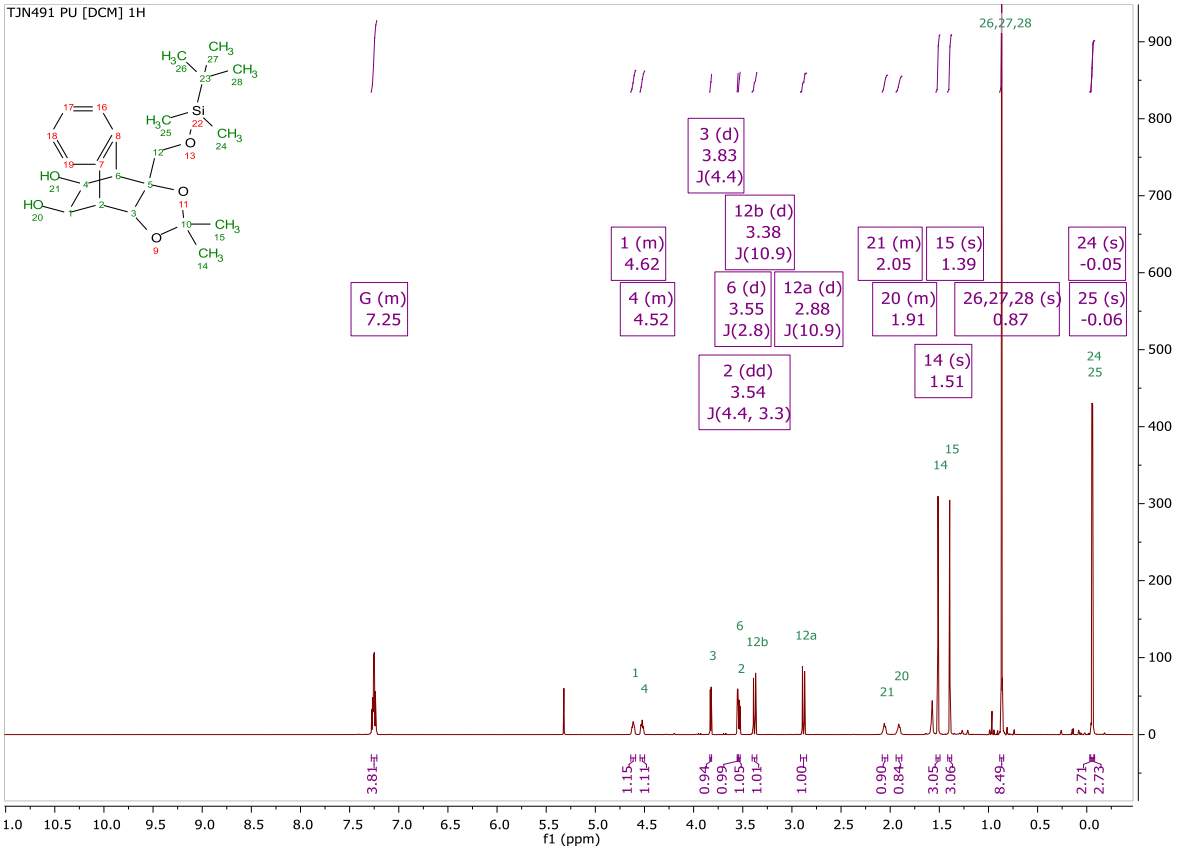
Sample-ID	tn_sel_TJN488	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN488_356579_66_01_62672.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	04/04/2018 11:03:20
Ionisation Mode	positive electrospray (ESI)		

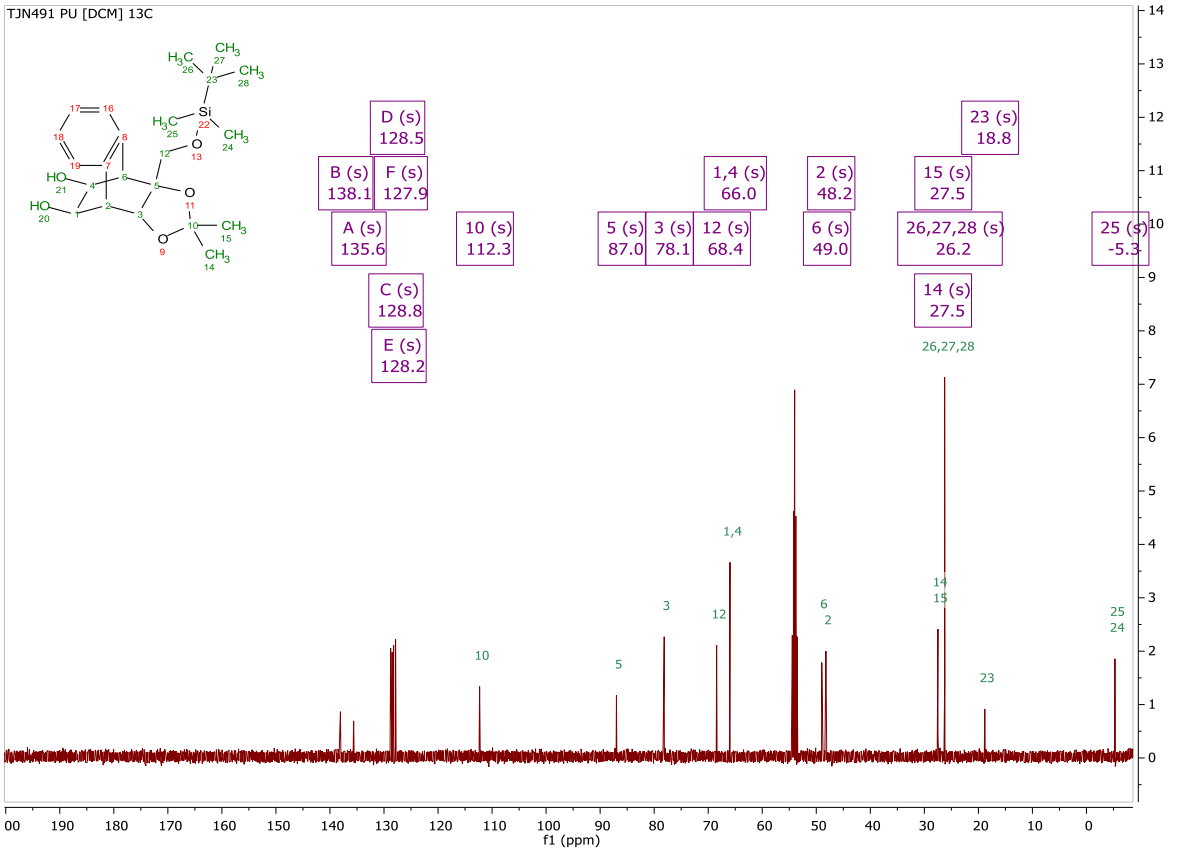
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

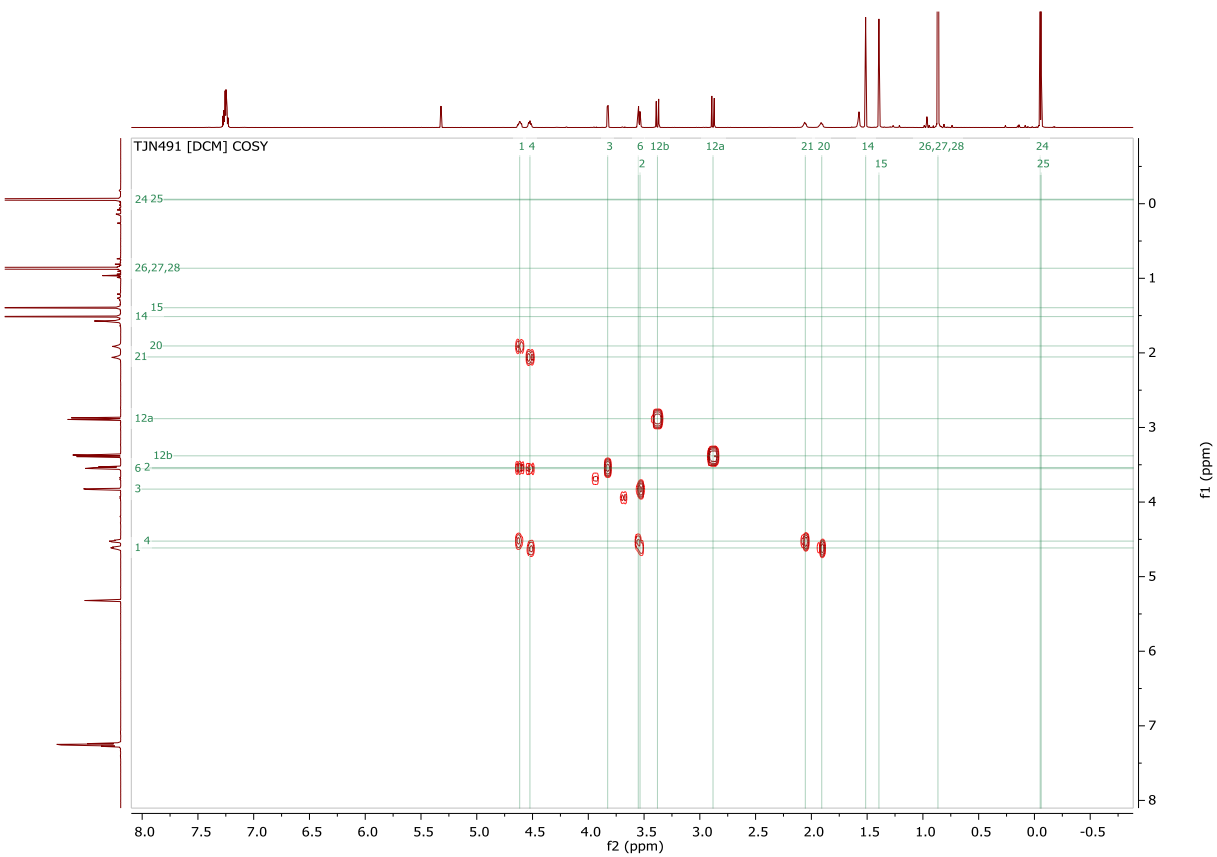


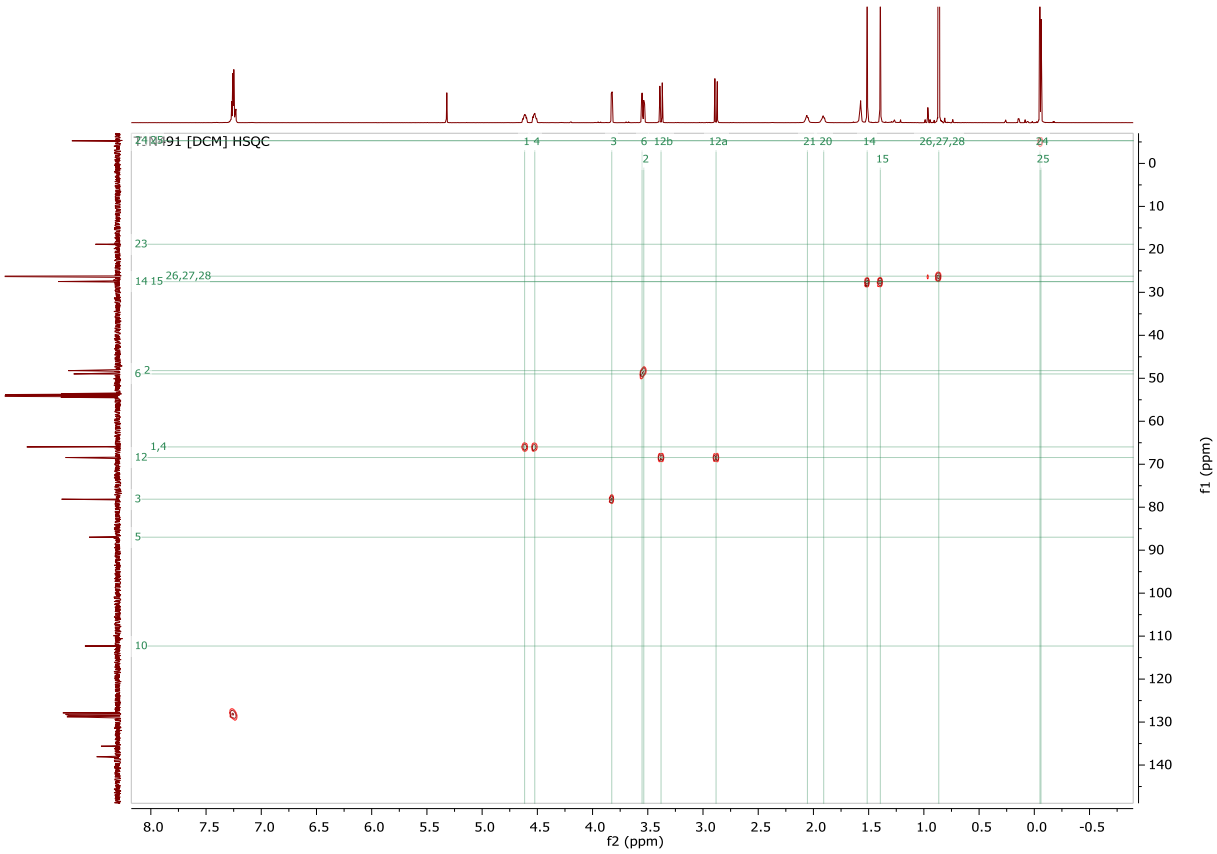
#	m/z	I	I %	Area	S/N
1	102.1303	3385	7.6	77	1433.7
2	107.0497	15683	35.0	103	5853.5
3	130.1612	4040	9.0	101	1630.4
4	219.1352	5272	11.8	208	634.2
5	236.0782	11657	26.0	129	1209.0
6	243.1358	8013	17.9	365	786.8
7	395.2030	44760	100.0	3163	3000.6
8	396.2048	12666	28.3	889	864.0
9	479.2553	13377	29.9	1143	1110.8
10	480.2582	3920	8.8	341	330.2

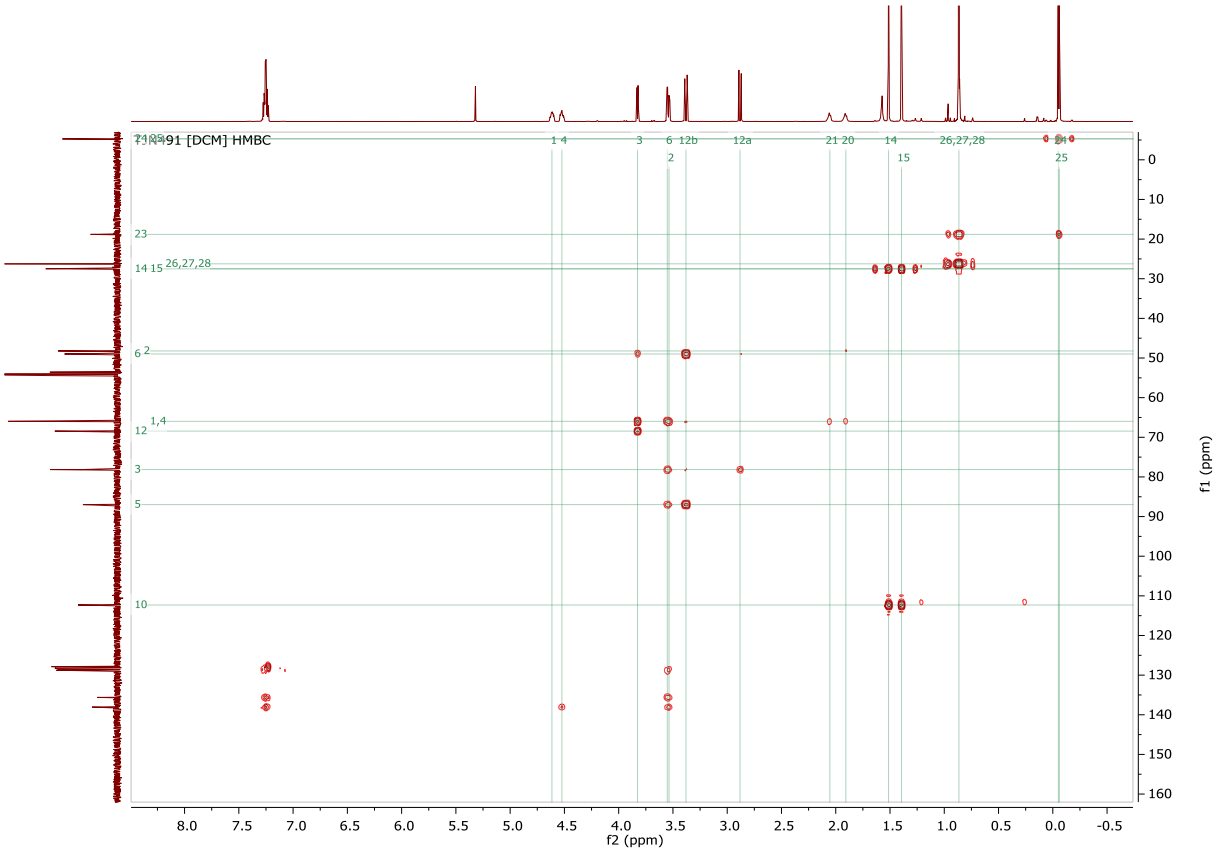
(3a*R*,4*S*,9*R*,9a*R*,10*S*,11*R*)-9a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-ethanonaphtho[2,3-d][1,3]dioxole-10,11-diol II-64






TJN491 [DCM] COSY
f2 (ppm)
f1 (ppm)

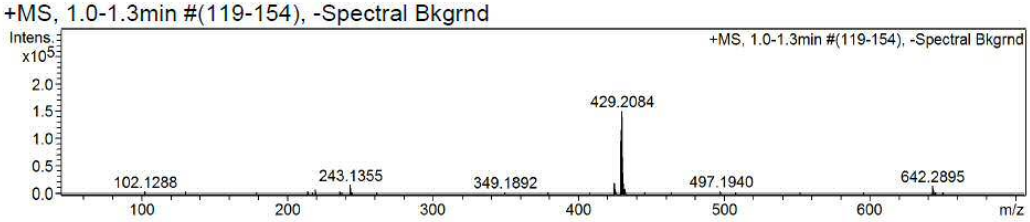

TJN491 [DCM] HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

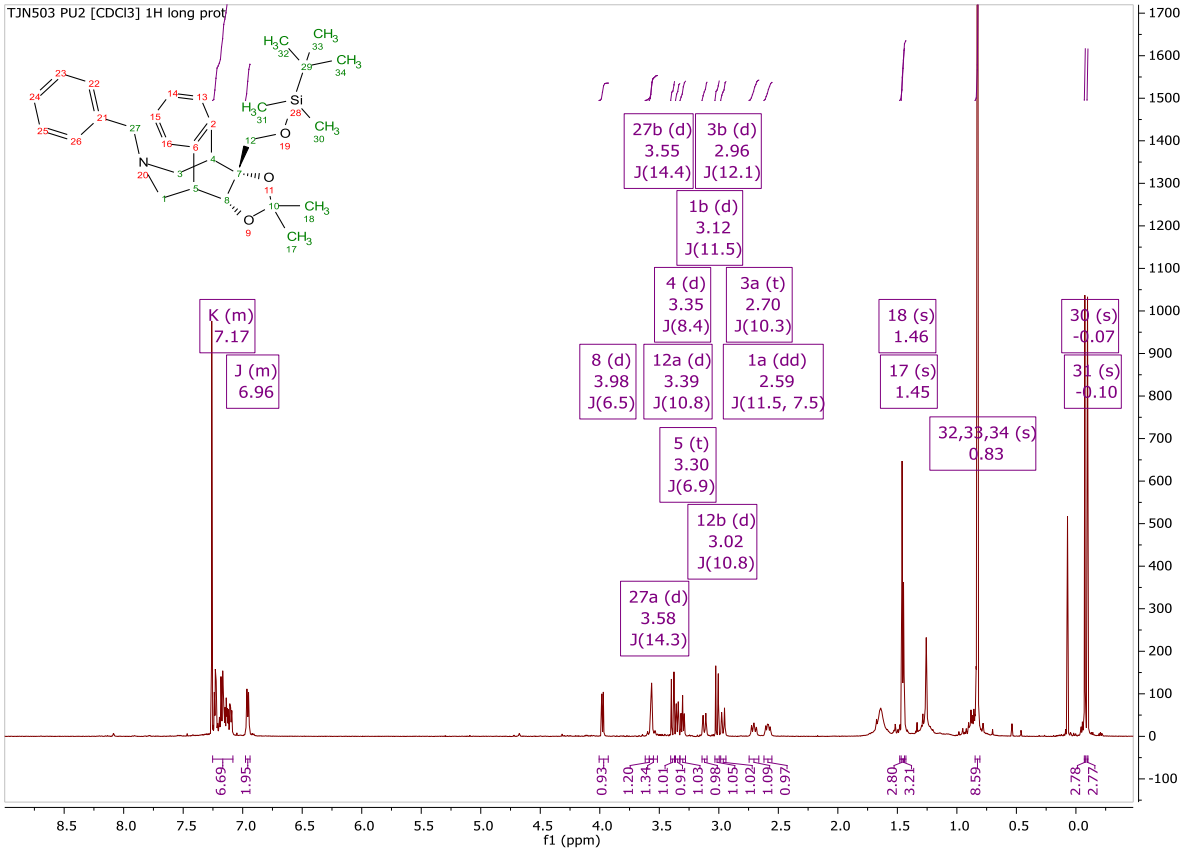
Sample-ID	tn_sel_TJN490	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN490_356680_59_01_62778.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	11/04/2018 16:45:05
Ionisation Mode	positive electrospray (ESI)		

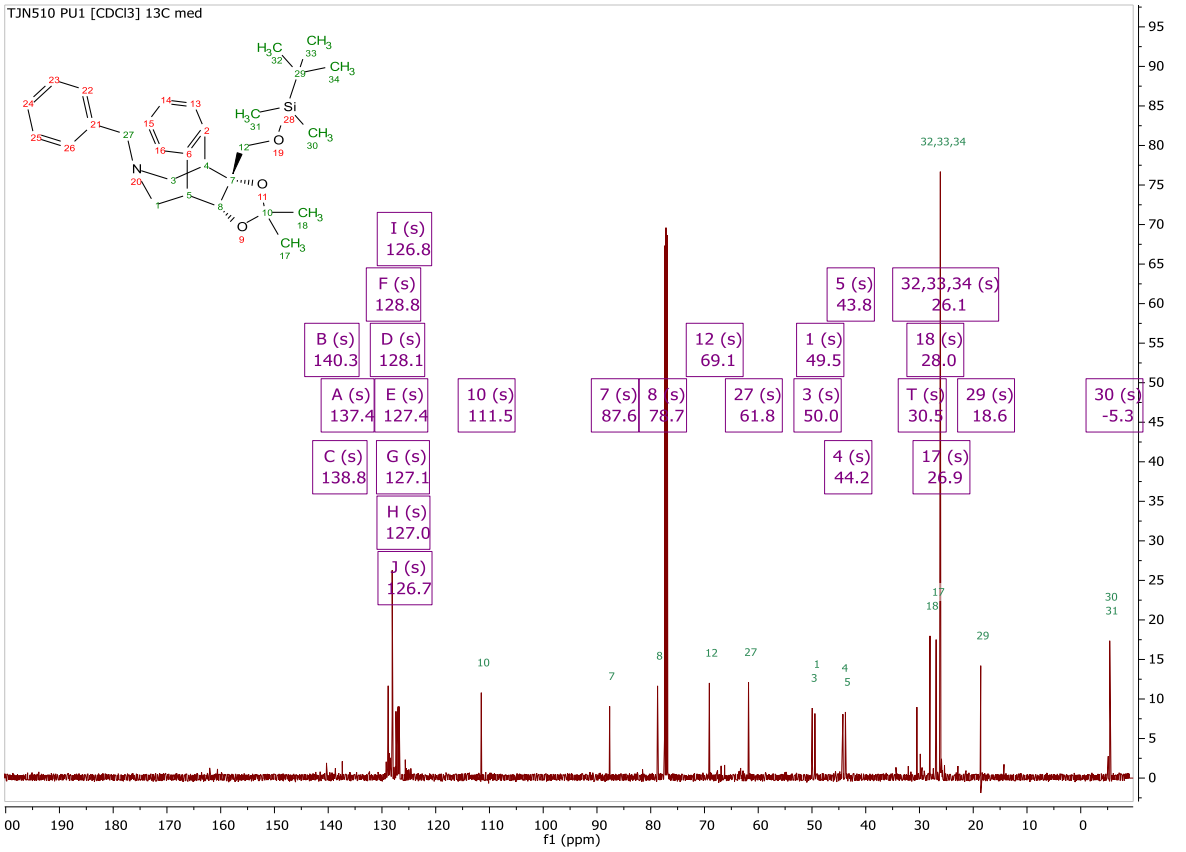
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

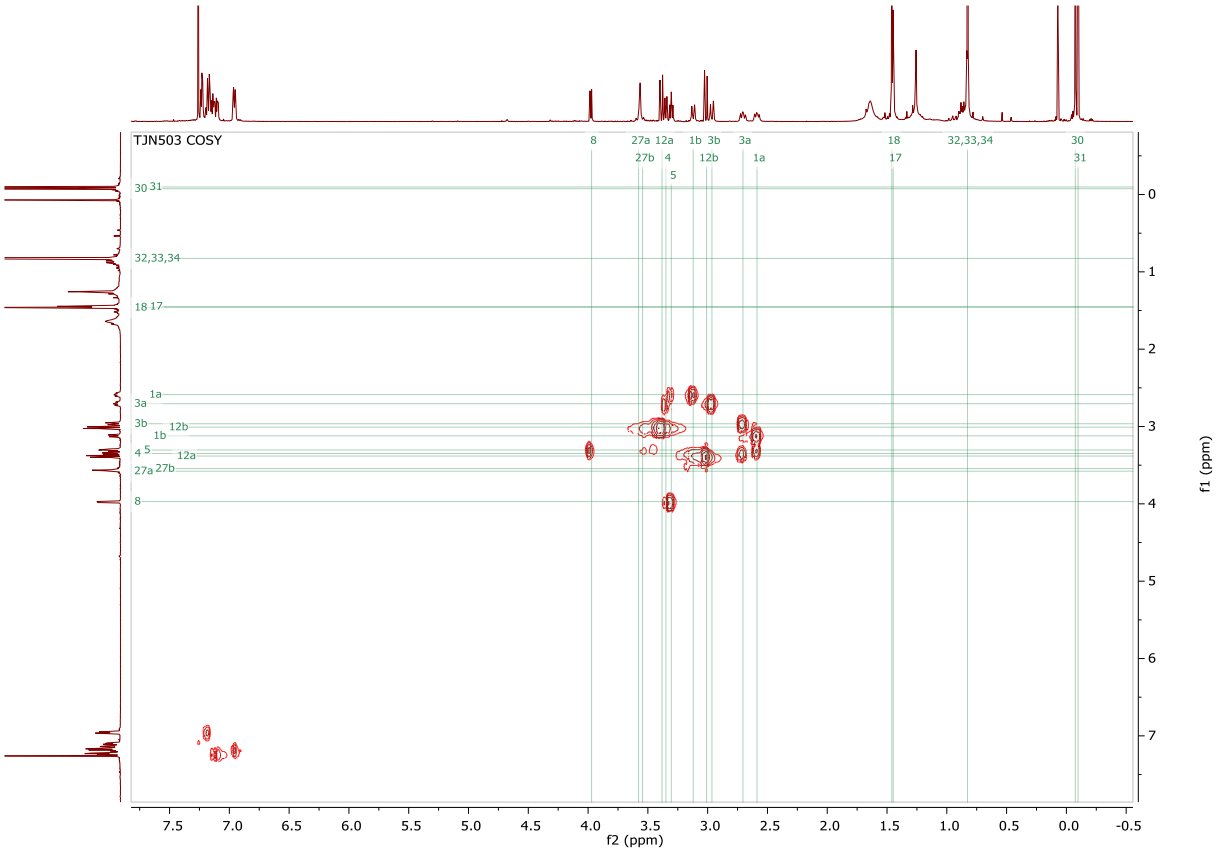


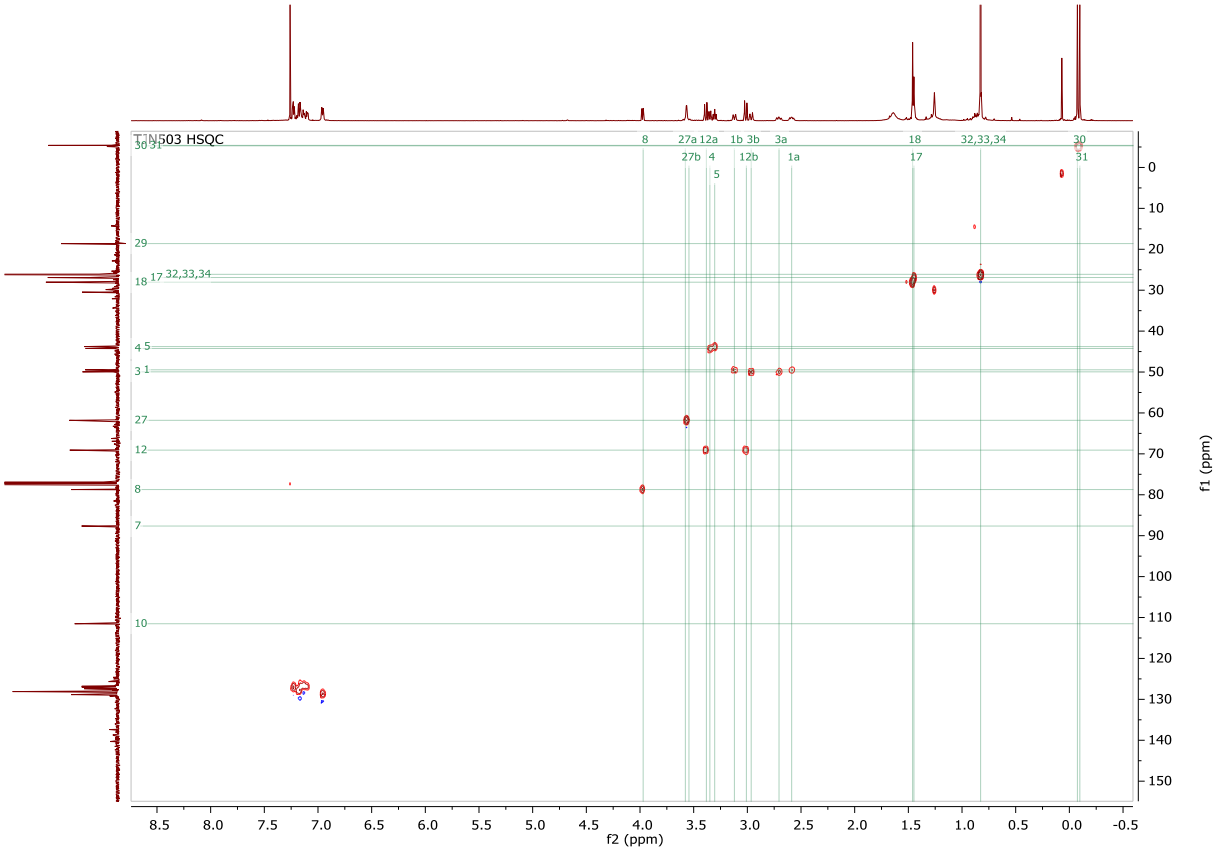
#	m/z	I	I %	Area	S/N
1	214.0980	4872	3.3	129	639.0
2	219.1357	6973	4.7	244	812.2
3	243.1355	15437	10.3	704	1174.6
4	424.2533	18826	12.6	1400	431.5
5	425.2555	5317	3.6	402	124.0
6	429.2084	149711	100.0	12006	3748.6
7	430.2120	42207	28.2	3039	1076.9
8	431.2133	9059	6.1	622	235.6
9	642.2895	13802	9.2	1665	658.9
10	643.2931	5837	3.9	668	282.4

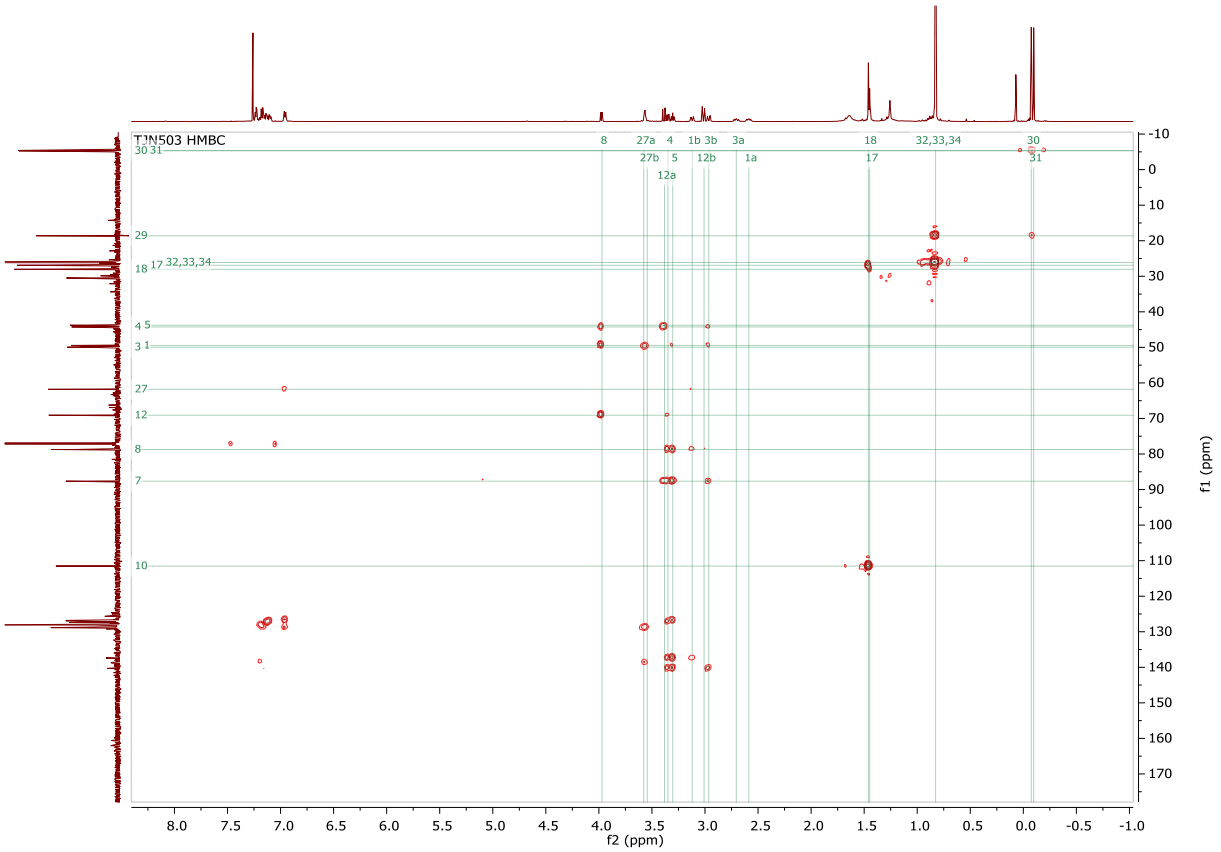
(3a*R*,4*R*)-11-benzyl-3a-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-(methanoiminomethano)naphtho[2,3-d][1,3]dioxole II-65






TJN503 COSY
f2 (ppm)
f1 (ppm)

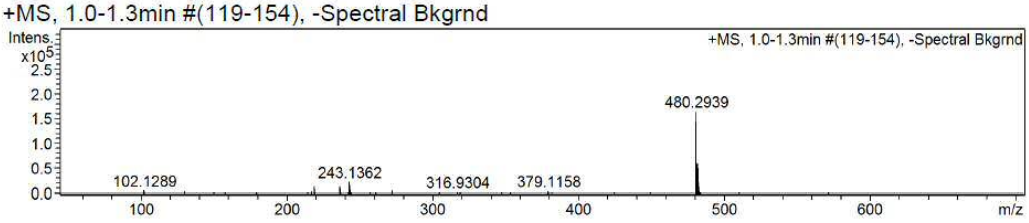

TJN503 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

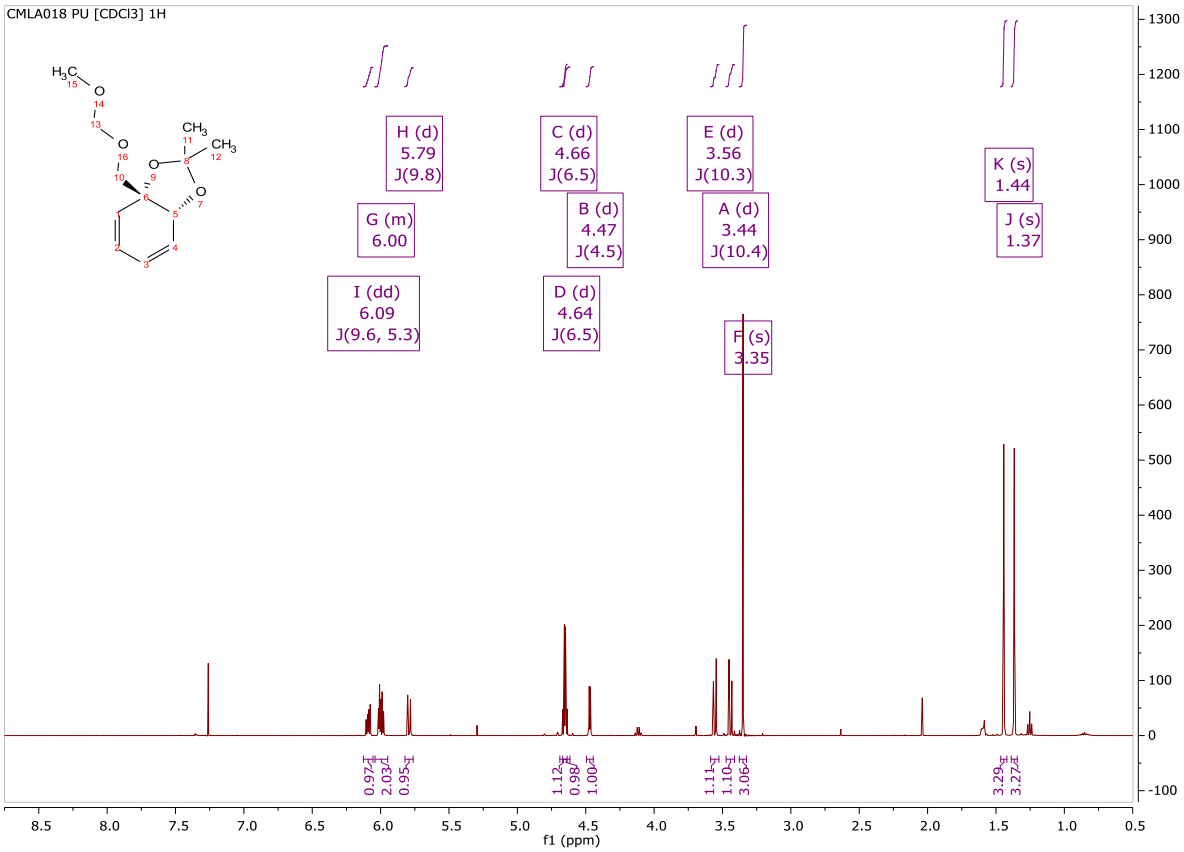
Sample-ID	tn_sel_TJN503	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN503_357166_39_01_63356.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	15/05/2018 13:54:08
Ionisation Mode	positive electrospray (ESI)		

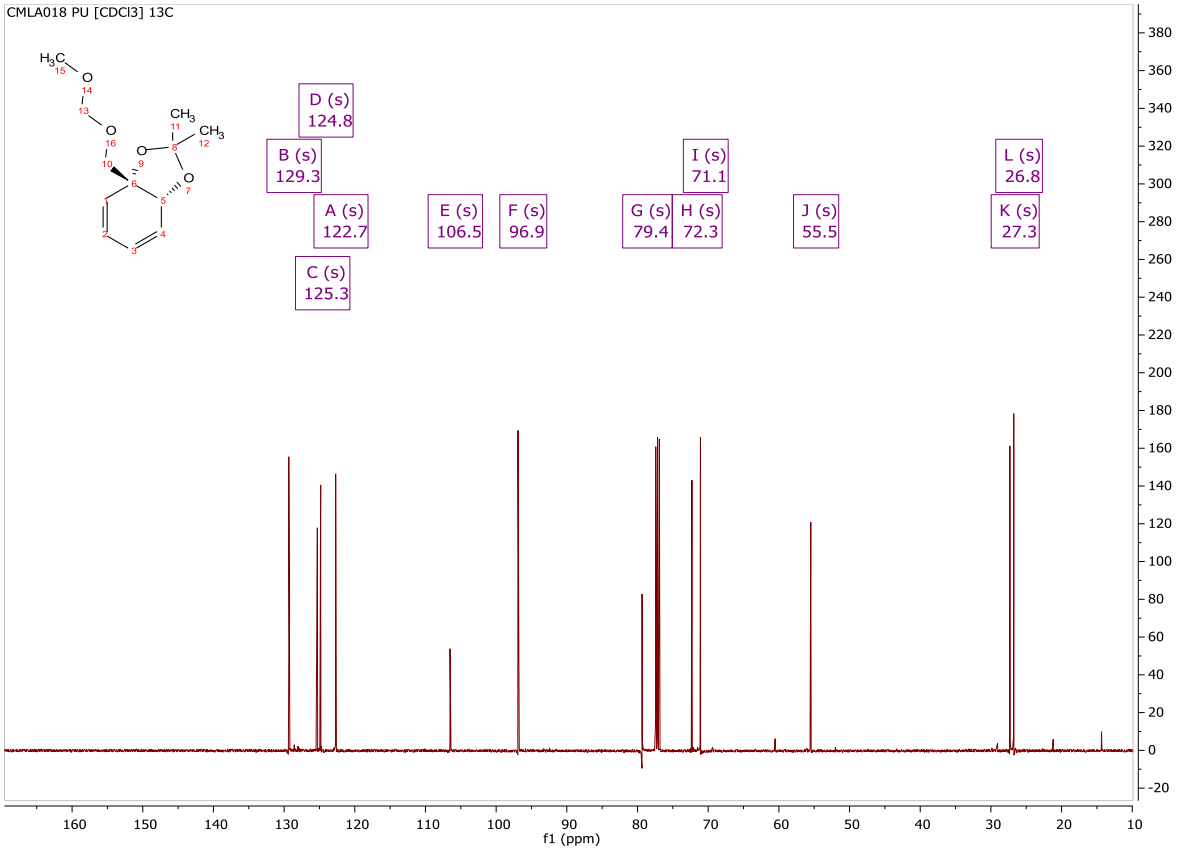
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	102.1289	5873	3.6	124	4095.5
2	217.1198	4406	2.7	158	428.9
3	219.1354	13037	7.9	436	1207.8
4	236.0980	13214	8.0	182	870.7
5	243.1362	23024	14.0	960	1360.7
6	272.1937	7331	4.5	99	462.3
7	379.1158	5275	3.2	318	344.5
8	480.2939	164567	100.0	14371	5267.5
9	481.2967	59196	36.0	5085	1939.3
10	482.2966	16125	9.8	1403	540.9

(3a*R*,7a*R*)-3a-((Methoxymethoxy)methyl)-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole II-66

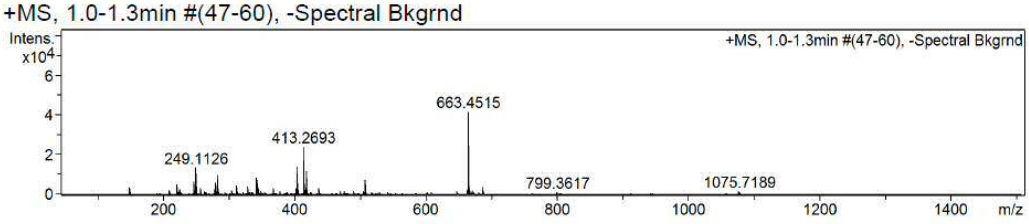




Confirmation of Expected Formula

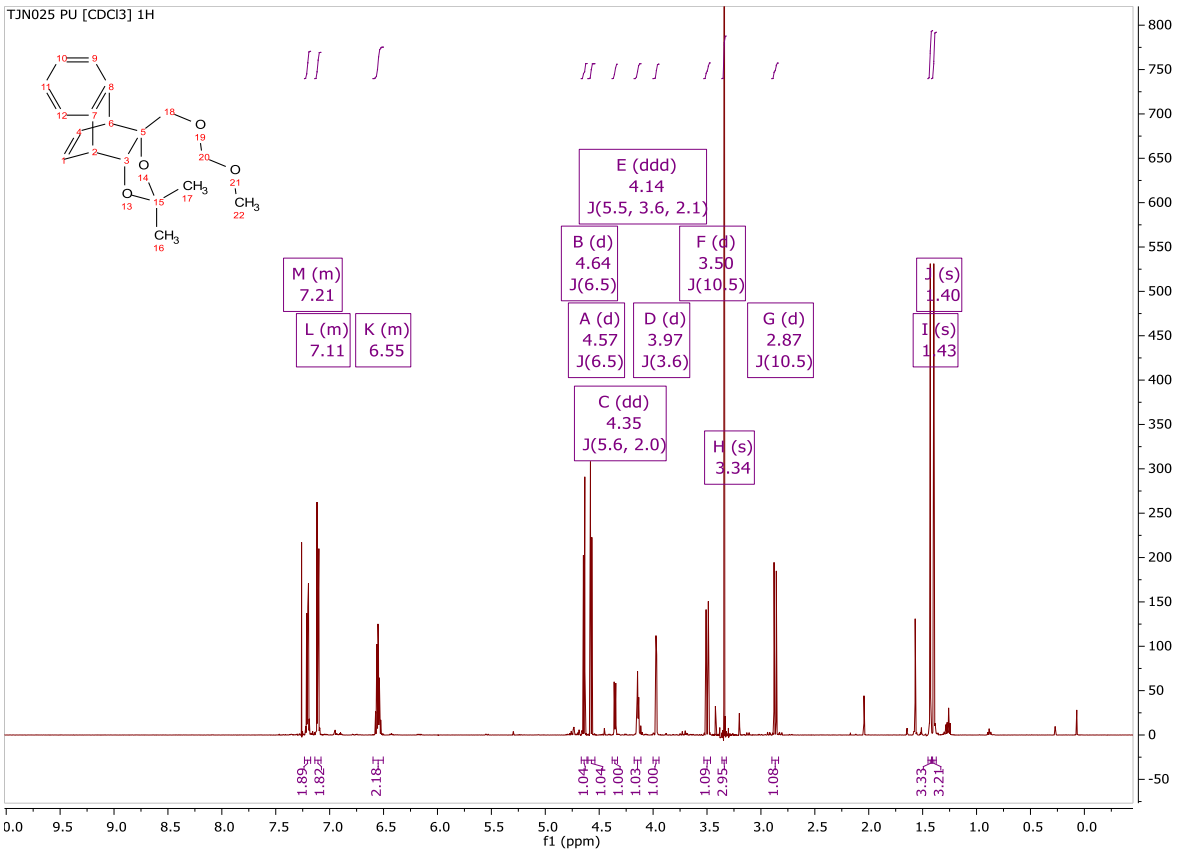
Sample-ID	ba_sel_CMLA018	Submitter	Ben Alexander
Analysis Name	ba_sel_CMLA018_343657_97_01_48045.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to1500 loop inj.m	Acquisition Date	29/04/2015 13:42:05
Ionisation Mode	positive electrospray (ESI)		

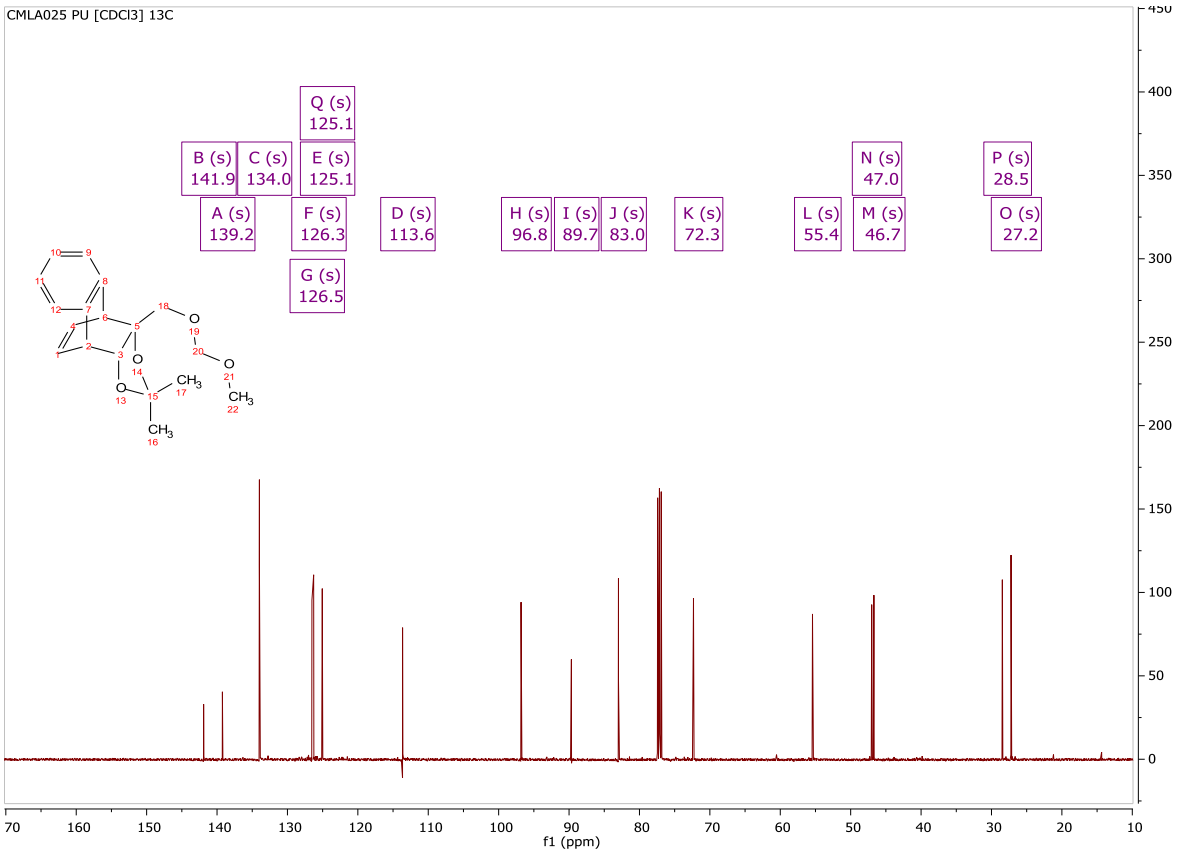
+MS, 1.0-1.3min #(47-60), -Spectral Bkgrnd

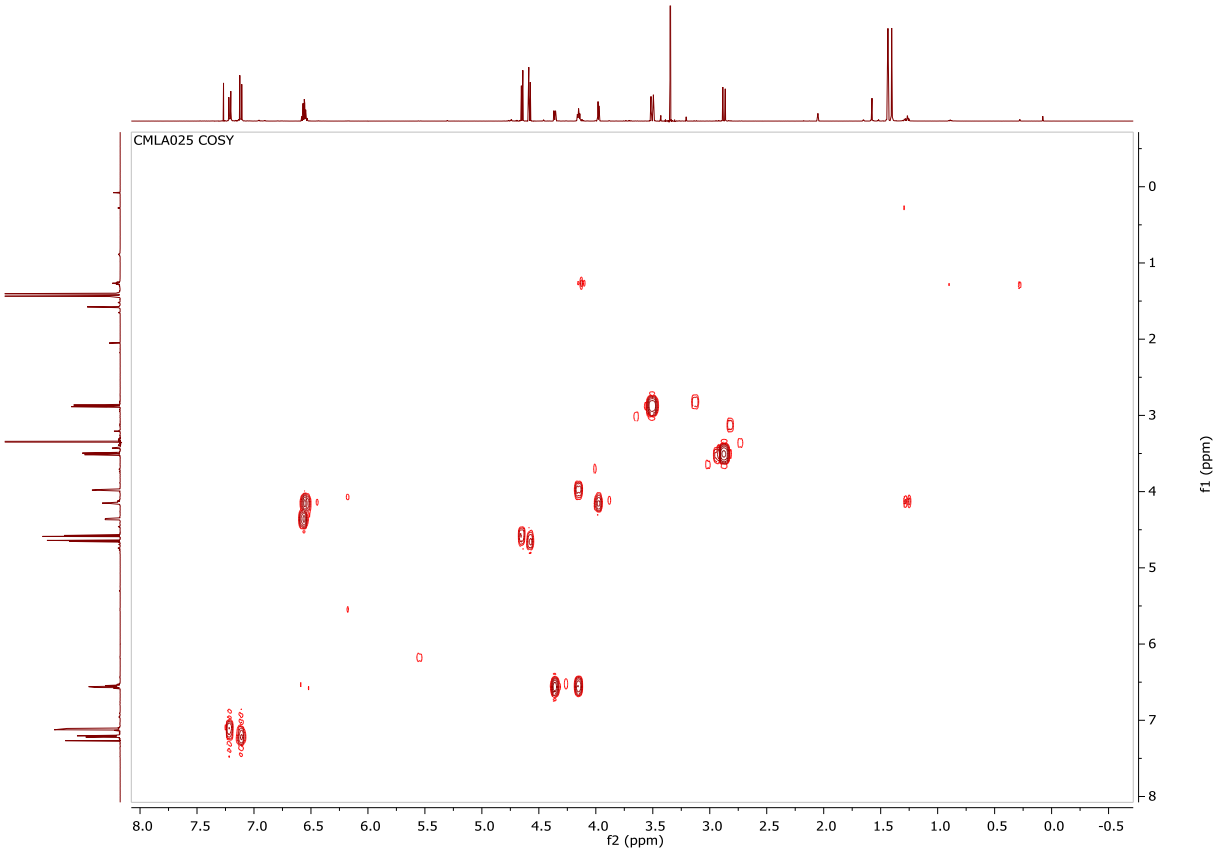


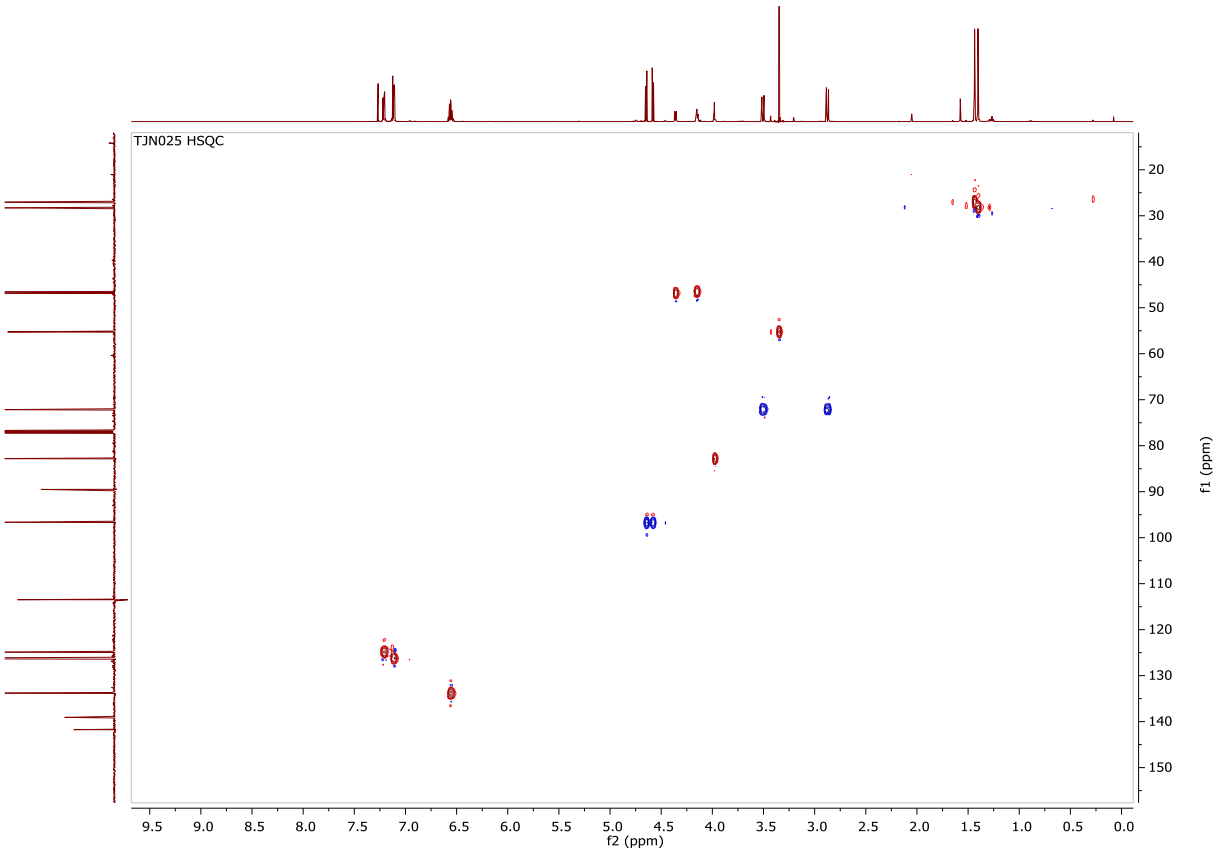
#	m/z	I	I %	Area	S/N
1	249.1126	13450	32.6	815	1055.3
2	282.2793	9838	23.8	627	552.7
3	341.1359	8153	19.7	571	362.7
4	343.1368	7488	18.1	529	331.0
5	403.2593	13782	33.4	1228	562.7
6	413.2693	23856	57.8	2037	1000.9
7	417.2748	11724	28.4	1125	497.4
8	506.5291	7204	17.4	594	394.4
9	663.4515	41291	100.0	4337	2421.5
10	664.4545	18456	44.7	2163	1080.9

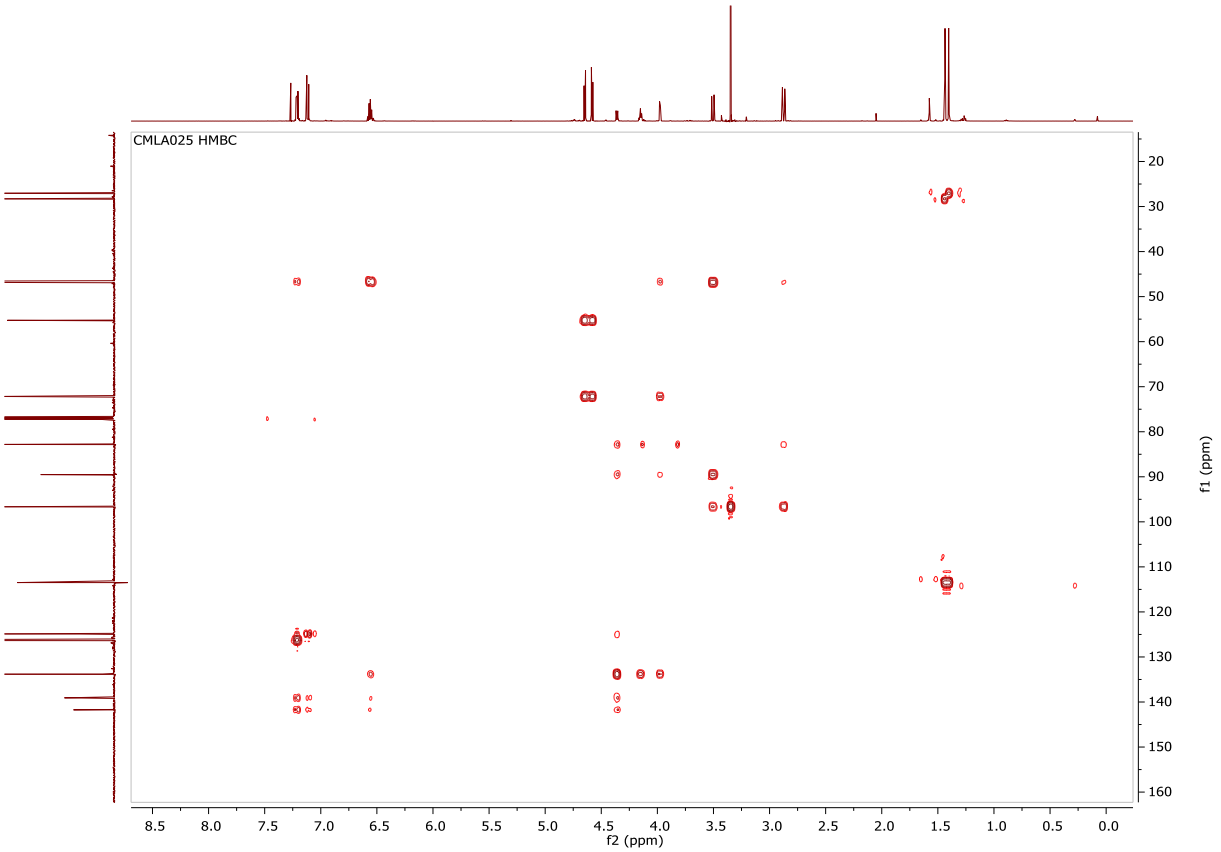
(3a*R*,4*S*,9*R*,9a*R*)-3a-((Methoxymethoxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-ethenonaphtho[2,3-d][1,3]dioxole II-67






CMLA025 COSY
f2 (ppm)
f1 (ppm)

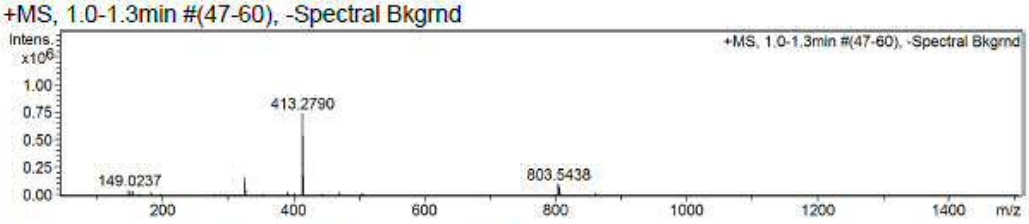

TJN025 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

Sample-ID	tn_sel_CMLA025	Submitter	Toby Nash
Analysis Name	tn_sel_CMLA025_343858_96_01_48270.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to1500 loop inj.m	Acquisition Date	20/05/2015 17:21:34
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(47-60), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	149.0237	46965	6.4	1111	5883.5
2	155.0843	35842	4.9	848	4058.3
3	325.1431	161013	21.8	8454	3516.5
4	326.1443	32918	4.5	2008	711.5
5	413.2790	738158	100.0	24656	11698.1
6	414.2717	193376	26.2	12336	3084.8
7	415.2726	30591	4.1	2780	491.3
8	469.3276	32312	4.4	3086	813.8
9	803.5438	104397	14.1	12991	2728.3
10	804.5438	67023	9.1	8510	1759.4

Generate Molecular Formula Parameters

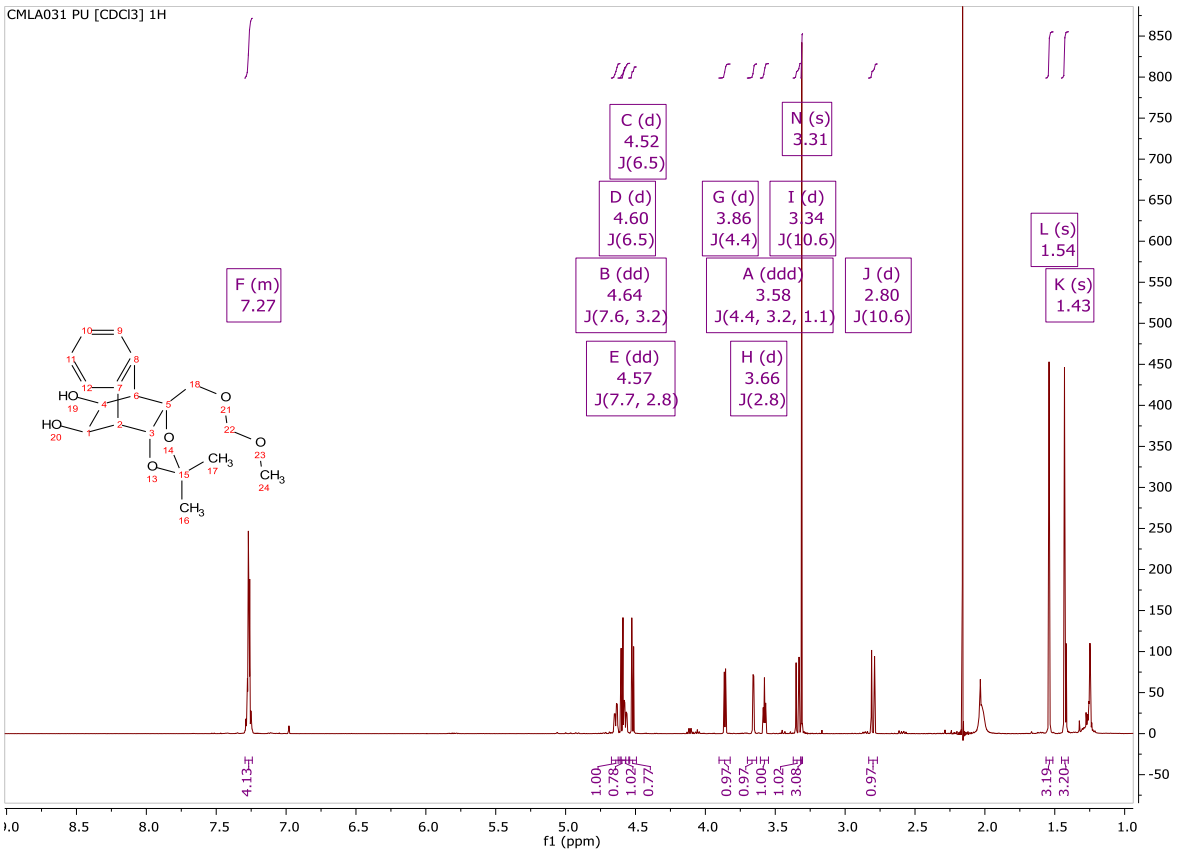
Charge	Tolerance	SearchRadius	H/C Ratio min.	H/C Ratio max.	Electron Conf.	Nitrogen Rule	sigma limit
positive	10 ppm	0.05 m/z	0	3	both	true	0.05

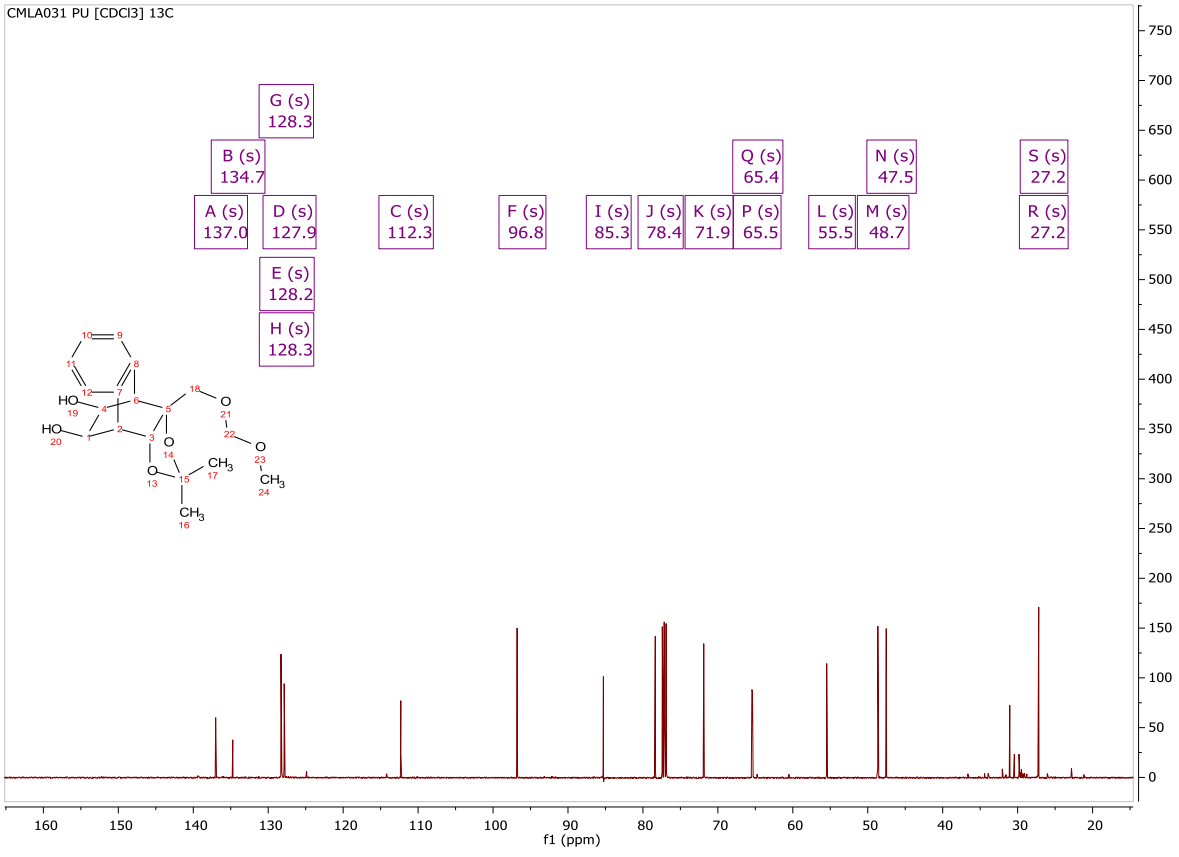
Expected Formula C18 H22 N0 O4 **Adduct(s):** H, Na

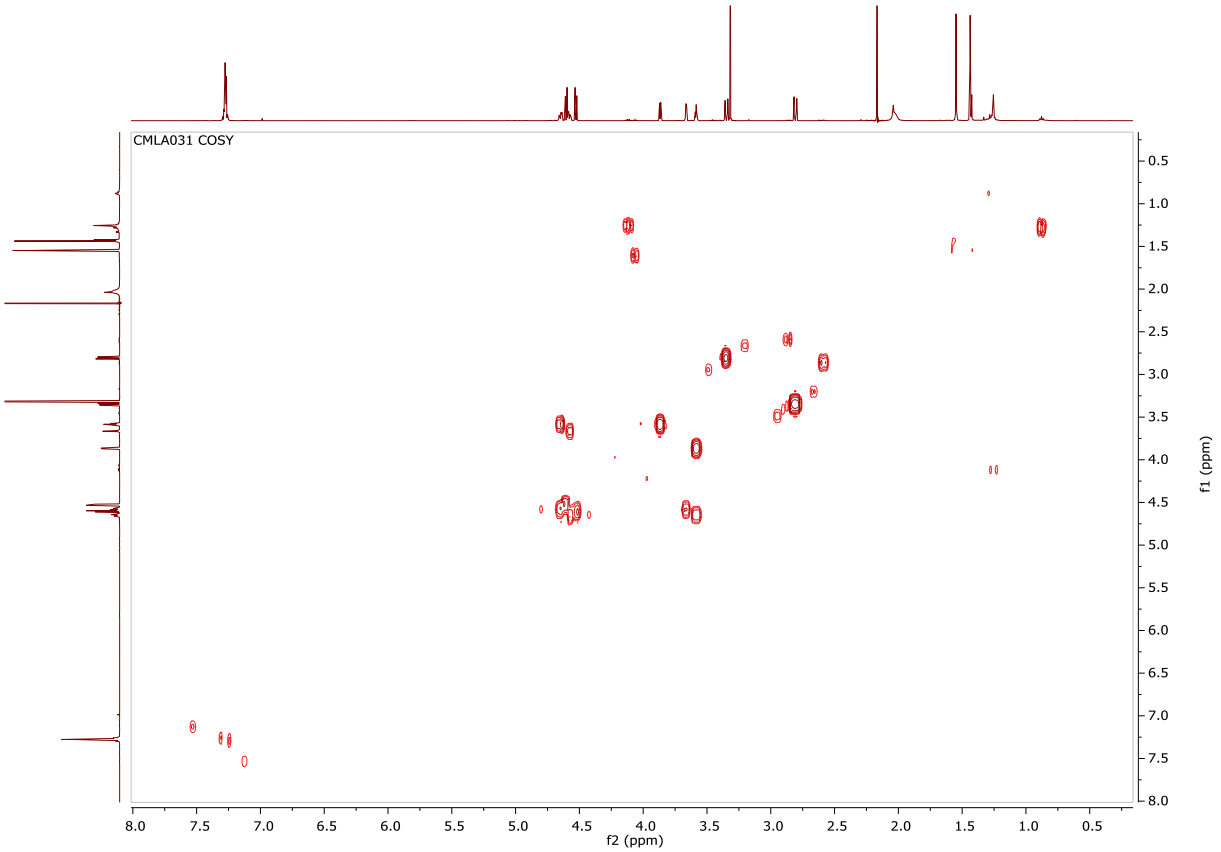
#	meas. m/z	theo. m/z	Err[ppm]	Sigma	Formula
1	325.1431	325.141579	-6.40	0.0059	C 18 H 22 Na 1 O 4

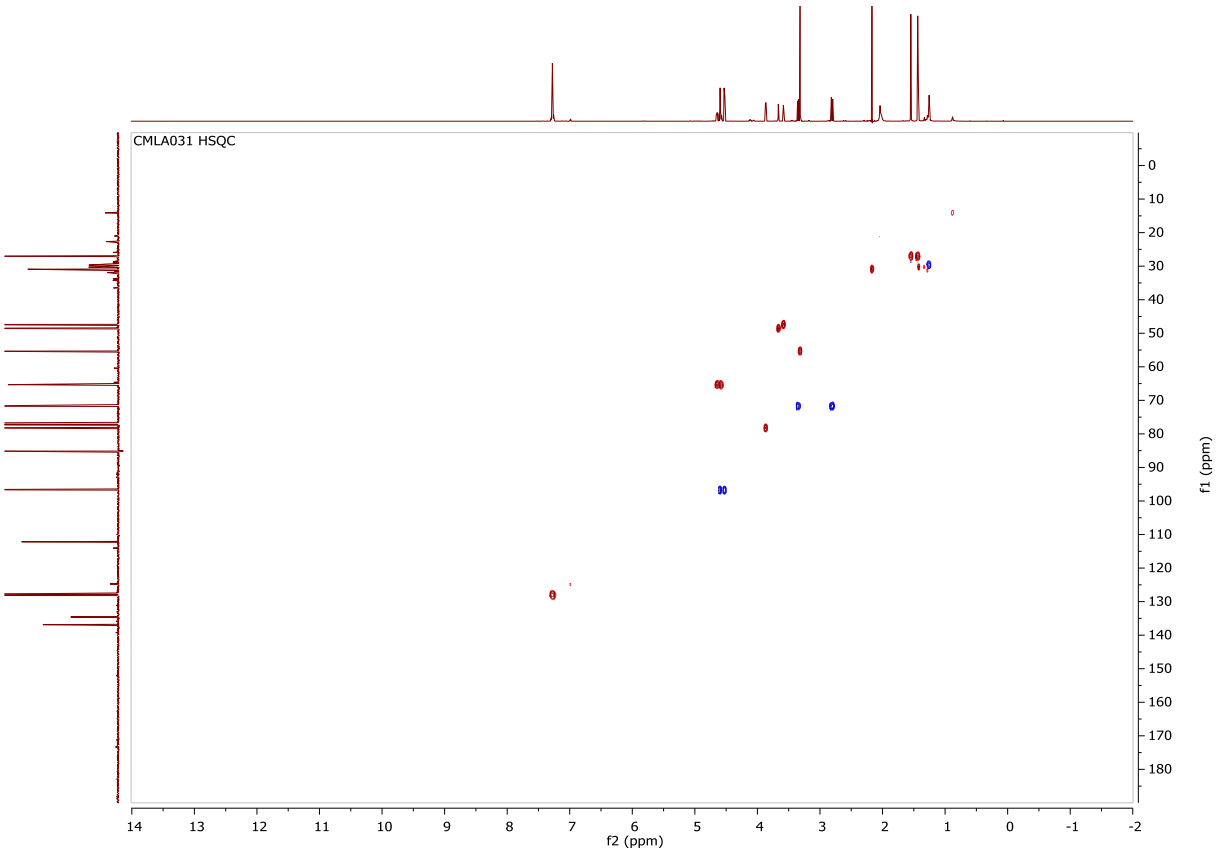
Note: Sigma fits < 0.05 indicates high probability of correct MF, and mass accuracy of 5ppm or better is generally acceptable for publication

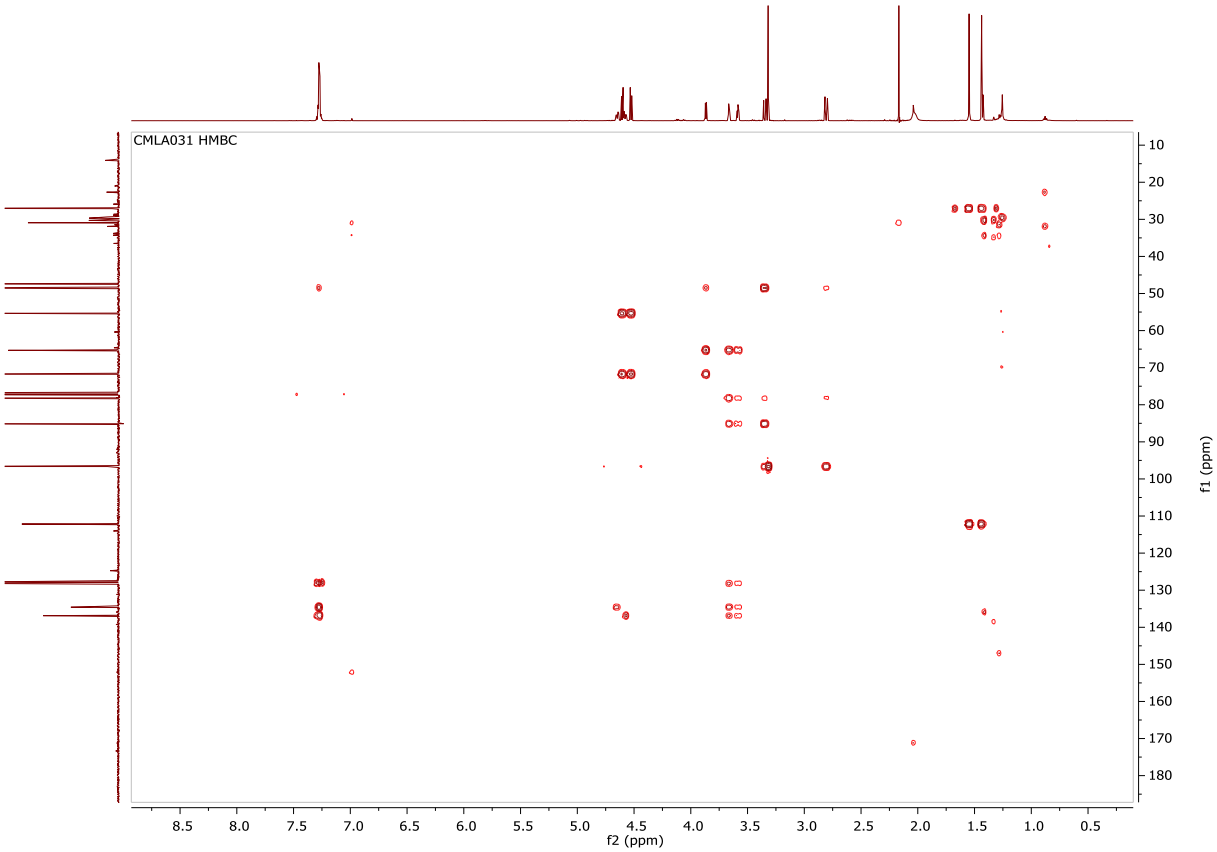
(3a*R*,4*S*,9*R*,9a*R*,10*S*,11*R*)-9a-((methoxymethoxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-ethanonaphtho[2,3-d][1,3]dioxole-10,11-diol II-68






CMLA031 COSY
f2 (ppm)
f1 (ppm)

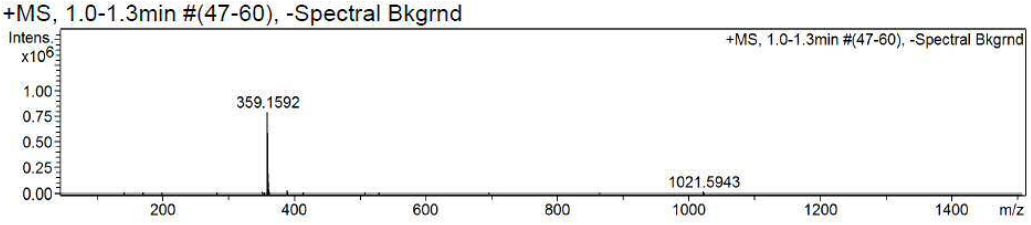

CMLA031 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

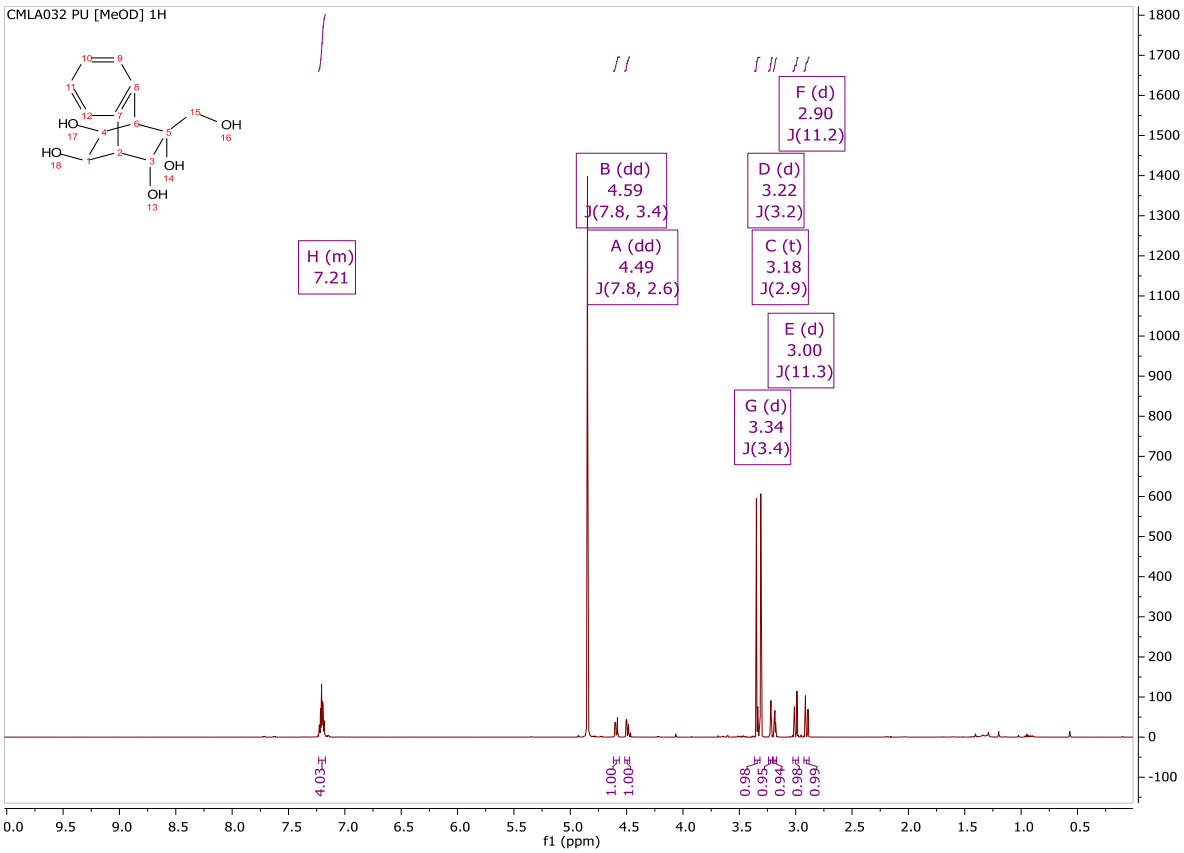
Sample-ID	tn_sel_CMLA031	Submitter	Toby Nash
Analysis Name	tn_sel_CMLA031_344041_95_01_48475.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to1500 loop inj.m	Acquisition Date	11/06/2015 11:56:47
Ionisation Mode	positive electrospray (ESI)		

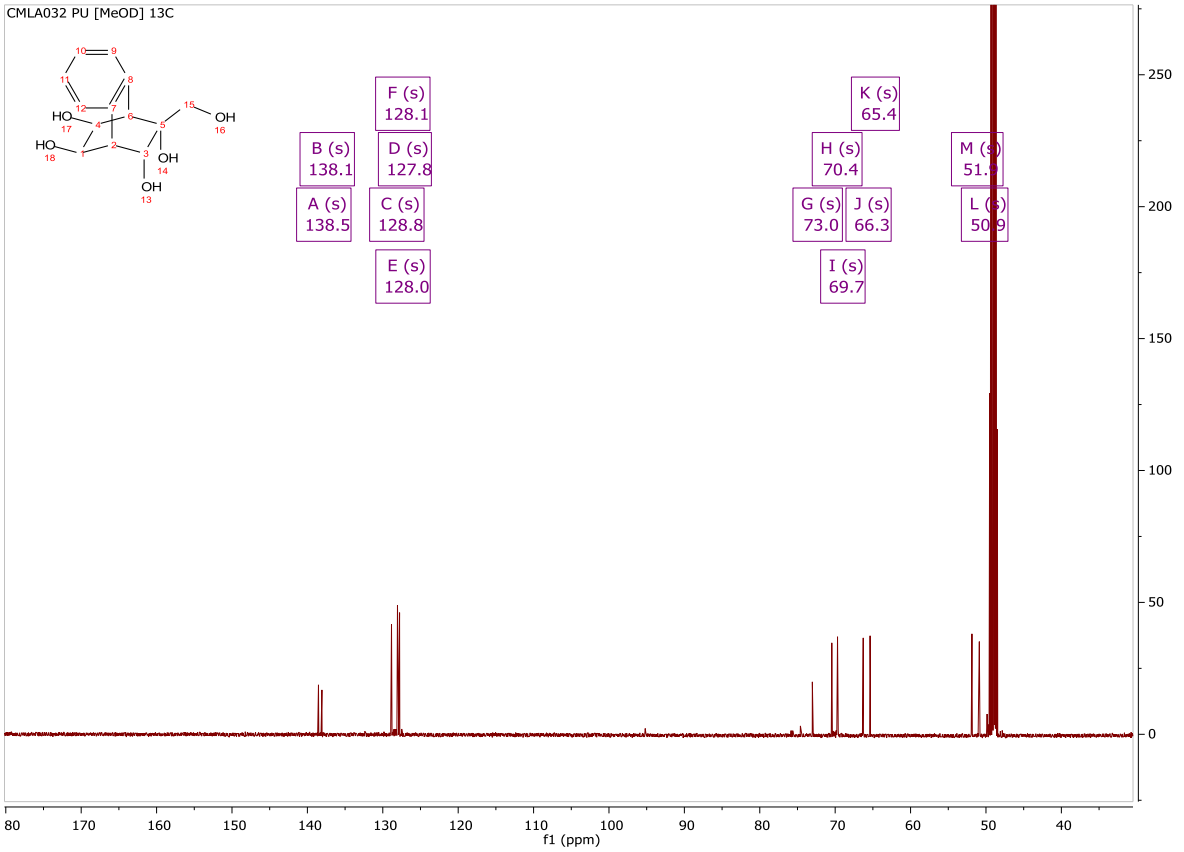
+MS, 1.0-1.3min #(47-60), -Spectral Bkgrnd

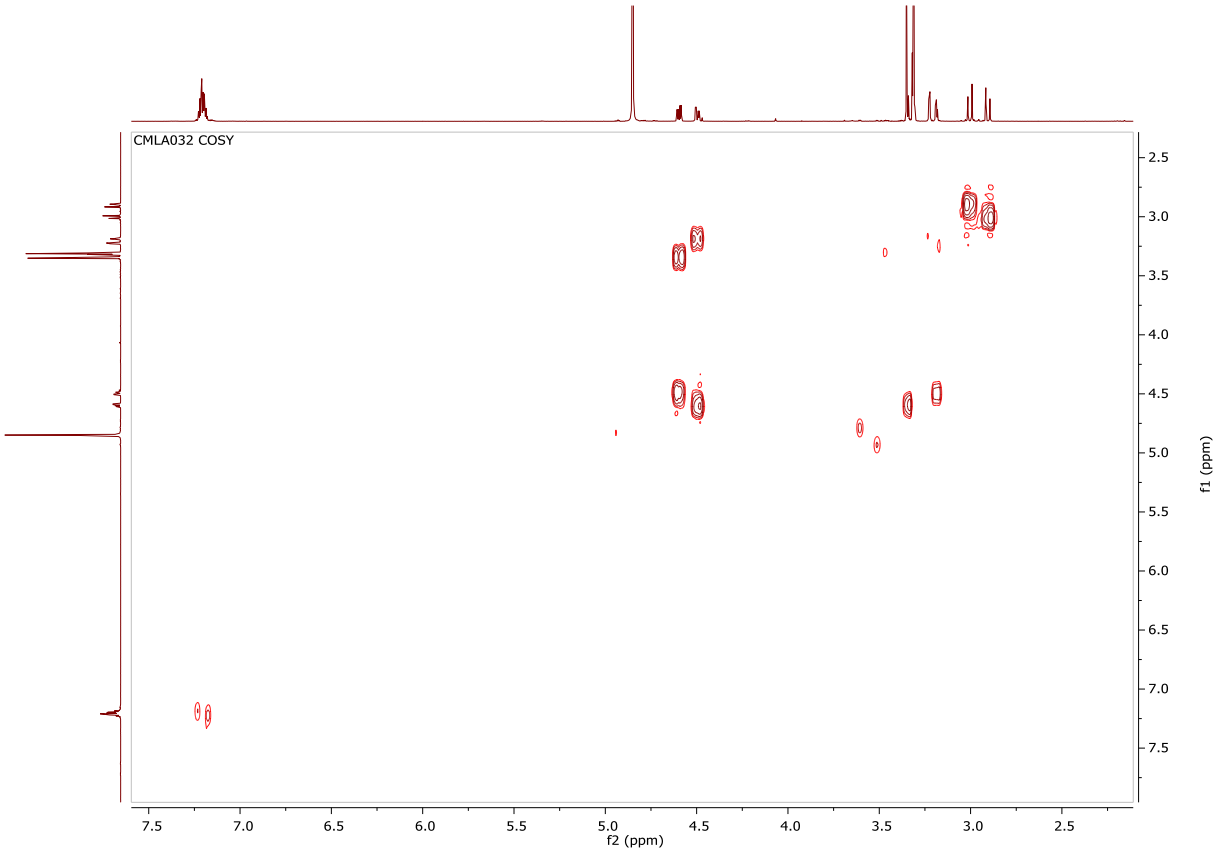


#	m/z	I	I %	Area	S/N
1	199.0774	13688	1.7	572	2190.0
2	351.1558	18850	2.4	534	296.0
3	359.1592	796323	100.0	27801	11410.7
4	360.1529	159819	20.1	10689	2265.5
5	361.1539	27125	3.4	2290	380.4
6	389.1578	31800	4.0	2717	361.1
7	413.2732	17250	2.2	1438	230.4
8	864.6650	12330	1.5	1856	374.1
9	1021.5943	22263	2.8	4031	822.8
10	1022.5962	14820	1.9	2596	547.1

(1*S*,2*R*,3*R*,4*R*,9*S*,10*R*)-3-(Hydroxymethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2,3,9,10-tetraol II-69



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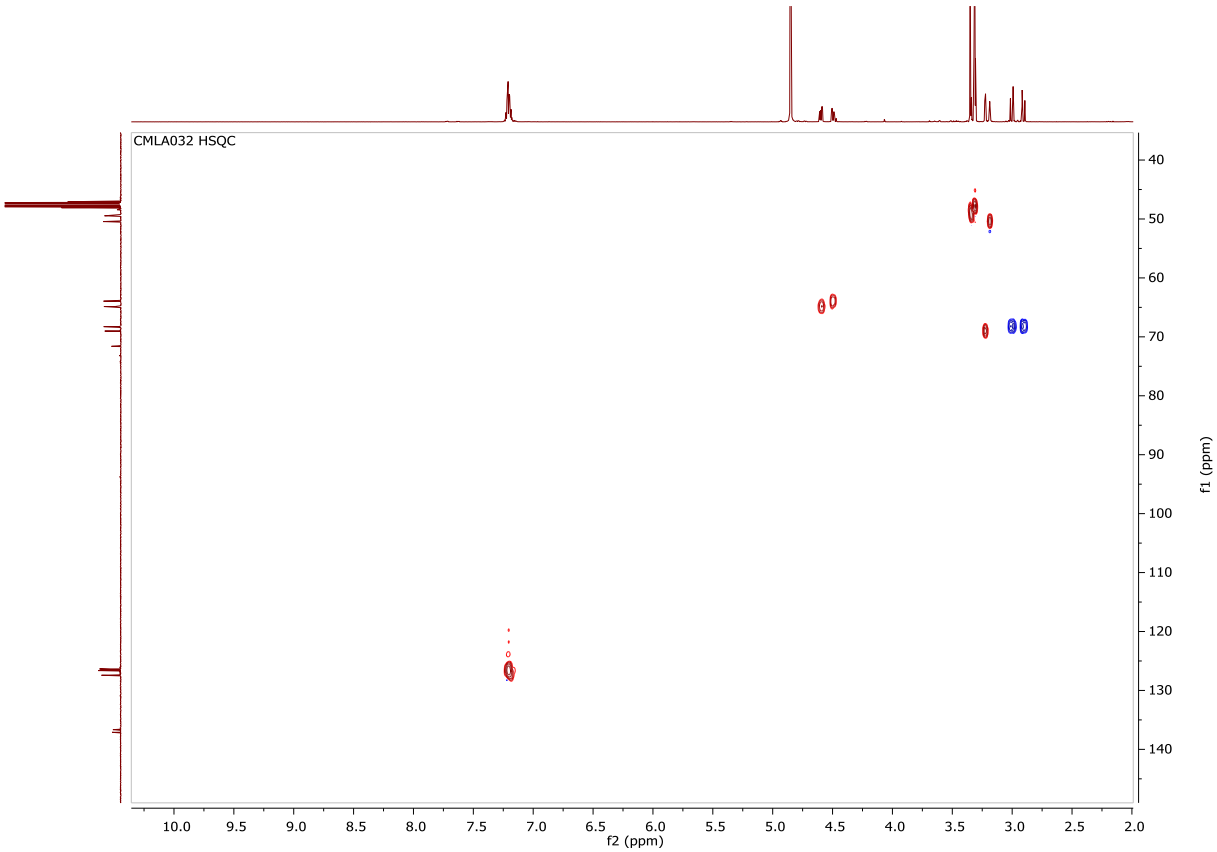
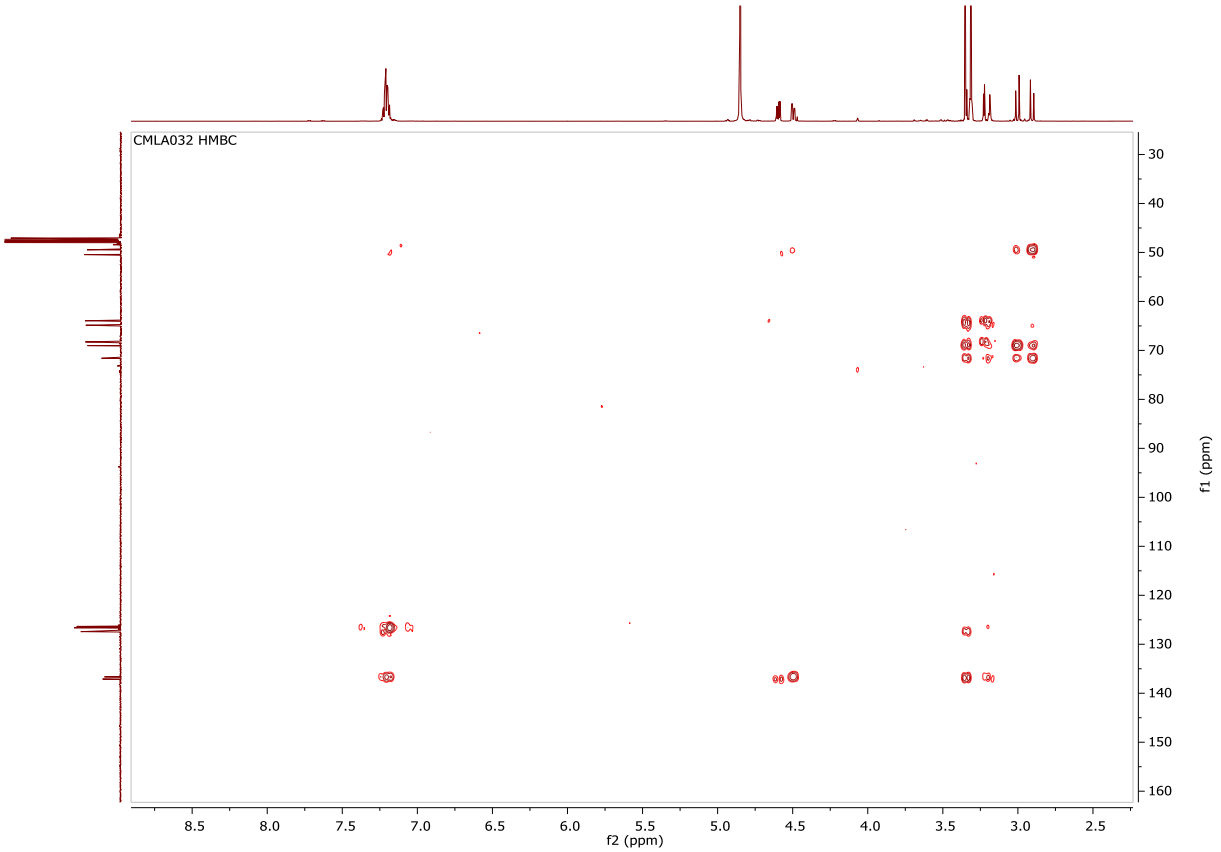
f1 (ppm)

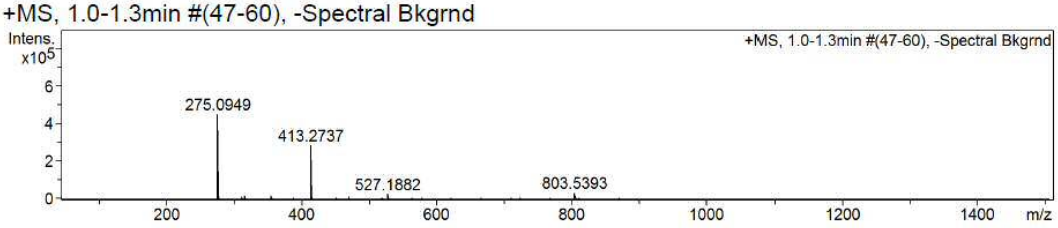

CMLA032 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

Sample-ID	tn_sel_CMLA032	Submitter	Toby Nash
Analysis Name	tn_sel_CMLA032_344070_26_01_48505.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to1500 loop inj.m	Acquisition Date	15/06/2015 16:54:40
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(47-60), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	275.0949	446983	100.0	16039	13286.9
2	276.0933	86695	19.4	5037	2548.0
3	277.0996	15899	3.6	1031	462.0
4	315.1281	15669	3.5	987	347.1
5	355.2823	19439	4.3	1454	354.9
6	413.2737	283095	63.3	14991	4460.7
7	414.2695	83403	18.7	6955	1313.1
8	527.1882	25865	5.8	3020	326.2
9	803.5393	33399	7.5	4641	305.8
10	804.5455	18016	4.0	2415	165.1

Crystal structure data for II-69

Table 1. Crystal data and structure refinement for s15sel4.

Identification code	s15sel4	
Empirical formula	C13 H18 O6	
Formula weight	270.27	
Temperature	150(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 7.21530(10) Å	α= 90°.
	b = 7.08780(10) Å	β= 92.9010(10)°.
	c = 12.35680(10) Å	γ = 90°.
Volume	631.124(13) $Å^3$	
Z	2	
Density (calculated)	1.422 Mg/m^3	
Absorption coefficient	0.952 mm^{-1}	
F(000)	288	
Crystal size	0.200 x 0.200 x 0.050 mm^3	
Theta range for data collection	3.582 to 72.581°.	
Index ranges	-8<=h<=8, -8<=k<=8, -13<=l<=15	
Reflections collected	12567	
Independent reflections	2502 [R(int) = 0.0213]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.84877	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2502 / 1 / 200	
Goodness-of-fit on F^2	1.078	
Final R indices [I>2sigma(I)]	R1 = 0.0235, wR2 = 0.0614	
R indices (all data)	R1 = 0.0236, wR2 = 0.0614	
Absolute structure parameter	-0.02(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.145 and -0.176 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for s15sel4. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7485(2)	6950(2)	7540(1)	17(1)
C(2)	6382(2)	5379(2)	6958(1)	13(1)
C(3)	6661(2)	3508(2)	7615(1)	16(1)
C(4)	4753(2)	2601(2)	7793(1)	15(1)
C(5)	3673(2)	2357(2)	6691(1)	14(1)
C(6)	3301(2)	4339(2)	6164(1)	14(1)
C(7)	4290(2)	5861(2)	6865(1)	13(1)
C(8)	3517(2)	5767(2)	7975(1)	14(1)
C(9)	2623(2)	7216(2)	8496(1)	18(1)
C(10)	1942(2)	6880(3)	9519(1)	22(1)
C(11)	2159(2)	5124(3)	10004(1)	25(1)
C(12)	3054(2)	3666(3)	9480(1)	22(1)
C(13)	3732(2)	3995(2)	8463(1)	15(1)
O(1)	7398(2)	8652(2)	6932(1)	22(1)
O(2)	6997(2)	5211(2)	5889(1)	18(1)
O(3)	7909(2)	2344(2)	7063(1)	25(1)
O(4)	1989(2)	1341(2)	6836(1)	19(1)
O(5)	1364(2)	4793(2)	6131(1)	17(1)
O(6)	-404(2)	3439(2)	4346(1)	19(1)

Table 3. Bond lengths [Å] for s15sel4.

C(1)-O(1)	1.421(2)
C(1)-C(2)	1.527(2)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-O(2)	1.4196(18)
C(2)-C(7)	1.546(2)
C(2)-C(3)	1.563(2)
C(3)-O(3)	1.421(2)
C(3)-C(4)	1.545(2)
C(3)-H(3)	1.0000
C(4)-C(13)	1.506(2)
C(4)-C(5)	1.544(2)
C(4)-H(4)	1.0000
C(5)-O(4)	1.4313(18)
C(5)-C(6)	1.566(2)
C(5)-H(5)	1.0000
C(6)-O(5)	1.4324(18)
C(6)-C(7)	1.537(2)
C(6)-H(6)	1.0000
C(7)-C(8)	1.508(2)
C(7)-H(7)	1.0000
C(8)-C(9)	1.388(2)
C(8)-C(13)	1.398(2)
C(9)-C(10)	1.400(2)
C(9)-H(9)	0.9500
C(10)-C(11)	1.387(3)
C(10)-H(10A)	0.9500
C(11)-C(12)	1.395(3)
C(11)-H(11)	0.9500
C(12)-C(13)	1.391(2)
C(12)-H(12)	0.9500
O(1)-H(1)	0.85(3)
O(2)-H(2A)	0.80(3)
O(3)-H(3A)	0.89(3)
O(4)-H(4A)	0.85(3)
O(5)-H(5A)	0.90(3)
O(6)-H(6A)	0.85(3)

O(6)-H(6B)	0.88(3)

Table 4. Bond angles [°] for s15sel4.

O(1)-C(1)-C(2)	111.22(13)
O(1)-C(1)-H(1A)	109.4
C(2)-C(1)-H(1A)	109.4
O(1)-C(1)-H(1B)	109.4
C(2)-C(1)-H(1B)	109.4
H(1A)-C(1)-H(1B)	108.0
O(2)-C(2)-C(1)	108.63(12)
O(2)-C(2)-C(7)	107.45(12)
C(1)-C(2)-C(7)	110.94(13)
O(2)-C(2)-C(3)	111.95(12)
C(1)-C(2)-C(3)	108.88(12)
C(7)-C(2)-C(3)	109.01(12)
O(3)-C(3)-C(4)	114.69(13)
O(3)-C(3)-C(2)	108.12(12)
C(4)-C(3)-C(2)	109.53(12)
O(3)-C(3)-H(3)	108.1
C(4)-C(3)-H(3)	108.1
C(2)-C(3)-H(3)	108.1
C(13)-C(4)-C(5)	108.66(12)
C(13)-C(4)-C(3)	105.63(13)
C(5)-C(4)-C(3)	109.58(12)
C(13)-C(4)-H(4)	110.9
C(5)-C(4)-H(4)	110.9
C(3)-C(4)-H(4)	110.9
O(4)-C(5)-C(4)	109.86(12)
O(4)-C(5)-C(6)	111.99(12)
C(4)-C(5)-C(6)	109.55(12)
O(4)-C(5)-H(5)	108.5
C(4)-C(5)-H(5)	108.5
C(6)-C(5)-H(5)	108.5
O(5)-C(6)-C(7)	106.43(12)
O(5)-C(6)-C(5)	111.10(12)
C(7)-C(6)-C(5)	109.30(12)
O(5)-C(6)-H(6)	110.0
C(7)-C(6)-H(6)	110.0
C(5)-C(6)-H(6)	110.0
C(8)-C(7)-C(6)	107.38(12)

C(8)-C(7)-C(2)	109.11(12)
C(6)-C(7)-C(2)	108.08(12)
C(8)-C(7)-H(7)	110.7
C(6)-C(7)-H(7)	110.7
C(2)-C(7)-H(7)	110.7
C(9)-C(8)-C(13)	120.52(14)
C(9)-C(8)-C(7)	126.22(14)
C(13)-C(8)-C(7)	113.24(13)
C(8)-C(9)-C(10)	119.07(15)
C(8)-C(9)-H(9)	120.5
C(10)-C(9)-H(9)	120.5
C(11)-C(10)-C(9)	120.36(16)
C(11)-C(10)-H(10A)	119.8
C(9)-C(10)-H(10A)	119.8
C(10)-C(11)-C(12)	120.61(15)
C(10)-C(11)-H(11)	119.7
C(12)-C(11)-H(11)	119.7
C(13)-C(12)-C(11)	119.15(17)
C(13)-C(12)-H(12)	120.4
C(11)-C(12)-H(12)	120.4
C(12)-C(13)-C(8)	120.28(15)
C(12)-C(13)-C(4)	126.25(15)
C(8)-C(13)-C(4)	113.46(13)
C(1)-O(1)-H(1)	103(2)
C(2)-O(2)-H(2A)	107.0(19)
C(3)-O(3)-H(3A)	110.2(16)
C(5)-O(4)-H(4A)	108.1(18)
C(6)-O(5)-H(5A)	104.5(18)
H(6A)-O(6)-H(6B)	109(3)

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for s15sel4. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	16(1)	13(1)	21(1)	-2(1)	0(1)	-3(1)
C(2)	13(1)	10(1)	16(1)	-1(1)	1(1)	-1(1)
C(3)	14(1)	12(1)	23(1)	1(1)	-1(1)	0(1)
C(4)	16(1)	12(1)	18(1)	2(1)	0(1)	-1(1)
C(5)	13(1)	12(1)	18(1)	-2(1)	1(1)	-2(1)
C(6)	14(1)	14(1)	15(1)	-1(1)	0(1)	0(1)
C(7)	13(1)	10(1)	14(1)	1(1)	0(1)	-1(1)
C(8)	12(1)	16(1)	14(1)	-2(1)	-1(1)	-3(1)
C(9)	15(1)	17(1)	20(1)	-3(1)	-2(1)	1(1)
C(10)	19(1)	29(1)	19(1)	-8(1)	1(1)	2(1)
C(11)	24(1)	36(1)	15(1)	-1(1)	3(1)	-2(1)
C(12)	24(1)	23(1)	18(1)	4(1)	1(1)	-3(1)
C(13)	15(1)	15(1)	16(1)	0(1)	-1(1)	-2(1)
O(1)	24(1)	11(1)	32(1)	-1(1)	7(1)	-3(1)
O(2)	19(1)	18(1)	18(1)	-2(1)	6(1)	2(1)
O(3)	19(1)	10(1)	48(1)	2(1)	10(1)	2(1)
O(4)	15(1)	13(1)	30(1)	-1(1)	1(1)	-4(1)
O(5)	13(1)	16(1)	22(1)	-1(1)	-4(1)	1(1)
O(6)	20(1)	14(1)	23(1)	-2(1)	-5(1)	2(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for s15sel4.

	x	y	z	U(eq)
H(1A)	6980	7171	8259	20
H(1B)	8796	6554	7654	20
H(3)	7253	3829	8341	19
H(4)	4901	1364	8177	18
H(5)	4456	1607	6203	17
H(6)	3765	4363	5415	17
H(7)	4085	7140	6538	15
H(9)	2477	8418	8163	21
H(10A)	1327	7860	9883	27
H(11)	1694	4912	10699	30
H(12)	3199	2464	9814	26
H(1)	8140(40)	8440(40)	6430(20)	43(7)
H(2A)	7580(40)	4250(40)	5870(20)	35(7)
H(3A)	7650(30)	1140(40)	7160(20)	35(7)
H(4A)	1140(40)	2130(40)	6935(19)	31(6)
H(5A)	890(40)	4210(40)	5530(20)	43(7)
H(6A)	-780(40)	2330(40)	4180(20)	36(7)
H(6B)	-1110(50)	4260(50)	3980(30)	54(9)

Table 7. Torsion angles [°] for s15sel4.

O(1)-C(1)-C(2)-O(2)	53.24(17)
O(1)-C(1)-C(2)-C(7)	-64.65(16)
O(1)-C(1)-C(2)-C(3)	175.39(12)
O(2)-C(2)-C(3)-O(3)	15.91(16)
C(1)-C(2)-C(3)-O(3)	-104.21(14)
C(7)-C(2)-C(3)-O(3)	134.64(13)
O(2)-C(2)-C(3)-C(4)	-109.72(14)
C(1)-C(2)-C(3)-C(4)	130.17(13)
C(7)-C(2)-C(3)-C(4)	9.02(16)
O(3)-C(3)-C(4)-C(13)	175.41(13)
C(2)-C(3)-C(4)-C(13)	-62.83(15)
O(3)-C(3)-C(4)-C(5)	-67.71(17)
C(2)-C(3)-C(4)-C(5)	54.05(16)
C(13)-C(4)-C(5)-O(4)	-71.05(16)
C(3)-C(4)-C(5)-O(4)	173.99(12)
C(13)-C(4)-C(5)-C(6)	52.37(16)
C(3)-C(4)-C(5)-C(6)	-62.58(16)
O(4)-C(5)-C(6)-O(5)	10.29(17)
C(4)-C(5)-C(6)-O(5)	-111.87(13)
O(4)-C(5)-C(6)-C(7)	127.43(14)
C(4)-C(5)-C(6)-C(7)	5.27(16)
O(5)-C(6)-C(7)-C(8)	60.28(15)
C(5)-C(6)-C(7)-C(8)	-59.78(15)
O(5)-C(6)-C(7)-C(2)	177.87(11)
C(5)-C(6)-C(7)-C(2)	57.81(15)
O(2)-C(2)-C(7)-C(8)	171.60(12)
C(1)-C(2)-C(7)-C(8)	-69.80(16)
C(3)-C(2)-C(7)-C(8)	50.09(16)
O(2)-C(2)-C(7)-C(6)	55.13(15)
C(1)-C(2)-C(7)-C(6)	173.73(13)
C(3)-C(2)-C(7)-C(6)	-66.38(15)
C(6)-C(7)-C(8)-C(9)	-120.55(16)
C(2)-C(7)-C(8)-C(9)	122.53(16)
C(6)-C(7)-C(8)-C(13)	57.85(16)
C(2)-C(7)-C(8)-C(13)	-59.06(16)
C(13)-C(8)-C(9)-C(10)	0.0(2)
C(7)-C(8)-C(9)-C(10)	178.35(14)

C(8)-C(9)-C(10)-C(11)	0.1(2)
C(9)-C(10)-C(11)-C(12)	-0.2(3)
C(10)-C(11)-C(12)-C(13)	0.1(3)
C(11)-C(12)-C(13)-C(8)	0.0(2)
C(11)-C(12)-C(13)-C(4)	179.04(15)
C(9)-C(8)-C(13)-C(12)	-0.1(2)
C(7)-C(8)-C(13)-C(12)	-178.60(14)
C(9)-C(8)-C(13)-C(4)	-179.24(14)
C(7)-C(8)-C(13)-C(4)	2.25(18)
C(5)-C(4)-C(13)-C(12)	121.91(16)
C(3)-C(4)-C(13)-C(12)	-120.59(16)
C(5)-C(4)-C(13)-C(8)	-58.99(16)
C(3)-C(4)-C(13)-C(8)	58.51(16)

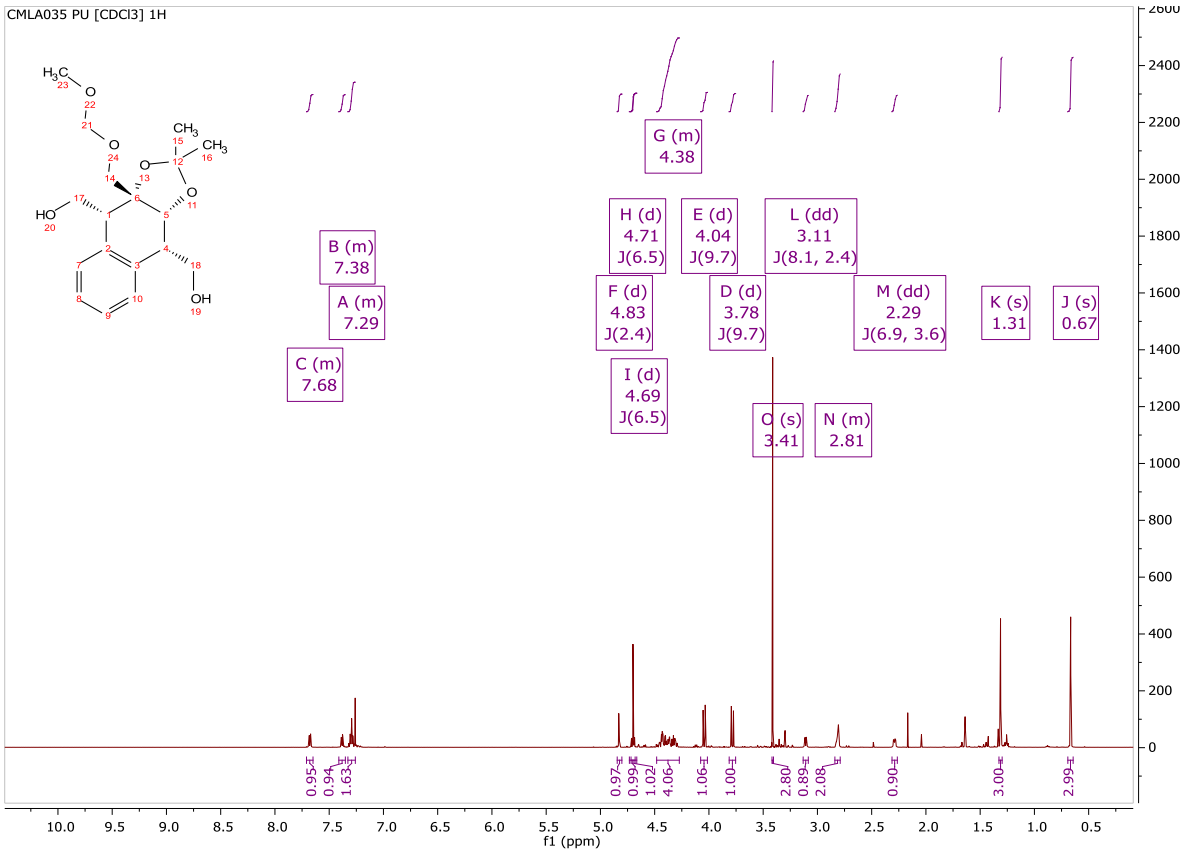
Table 8. Hydrogen bonds for s15sel4 [Å and °].

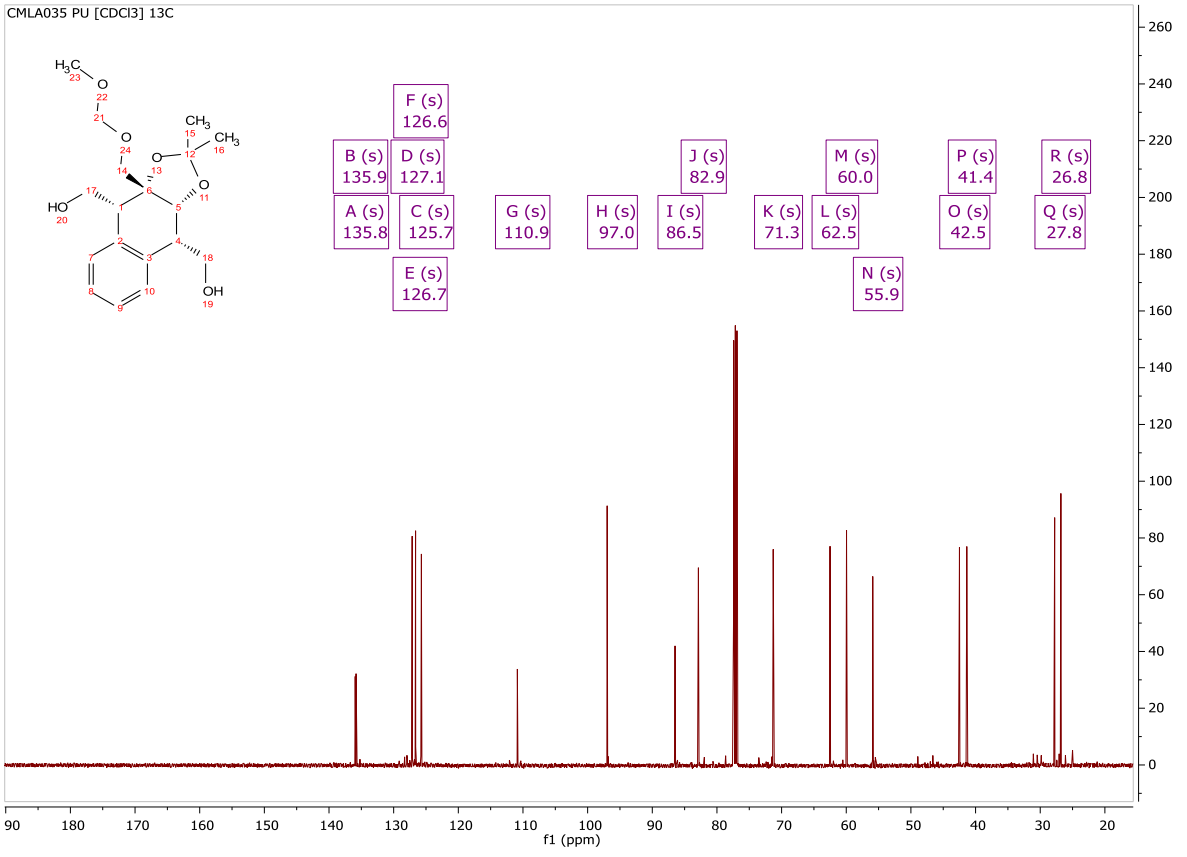
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(6)#1	0.85(3)	1.94(3)	2.7506(18)	160(3)
O(2)-H(2A)...O(3)	0.80(3)	2.01(3)	2.5626(18)	126(2)
O(2)-H(2A)...O(6)#2	0.80(3)	2.50(3)	3.0148(16)	123(2)
O(3)-H(3A)...O(1)#3	0.89(3)	1.79(3)	2.6471(17)	161(2)
O(4)-H(4A)...O(3)#4	0.85(3)	2.35(3)	3.0555(16)	141(2)
O(4)-H(4A)...O(5)	0.85(3)	2.14(3)	2.6281(17)	116(2)
O(5)-H(5A)...O(6)	0.90(3)	1.79(3)	2.6698(16)	168(3)
O(6)-H(6A)...O(5)#5	0.85(3)	1.88(3)	2.7322(17)	174(3)
O(6)-H(6B)...O(4)#6	0.88(3)	1.88(3)	2.7392(17)	165(3)

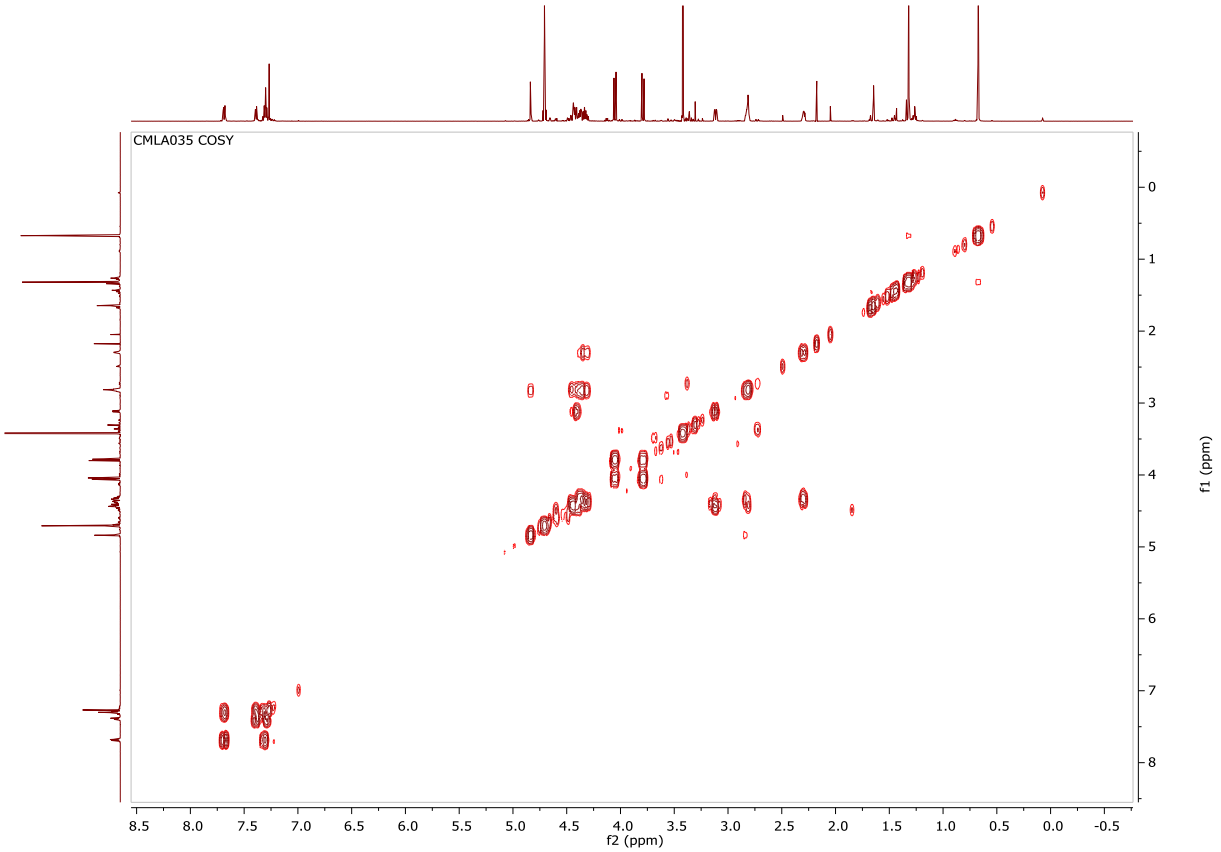
Symmetry transformations used to generate equivalent atoms:

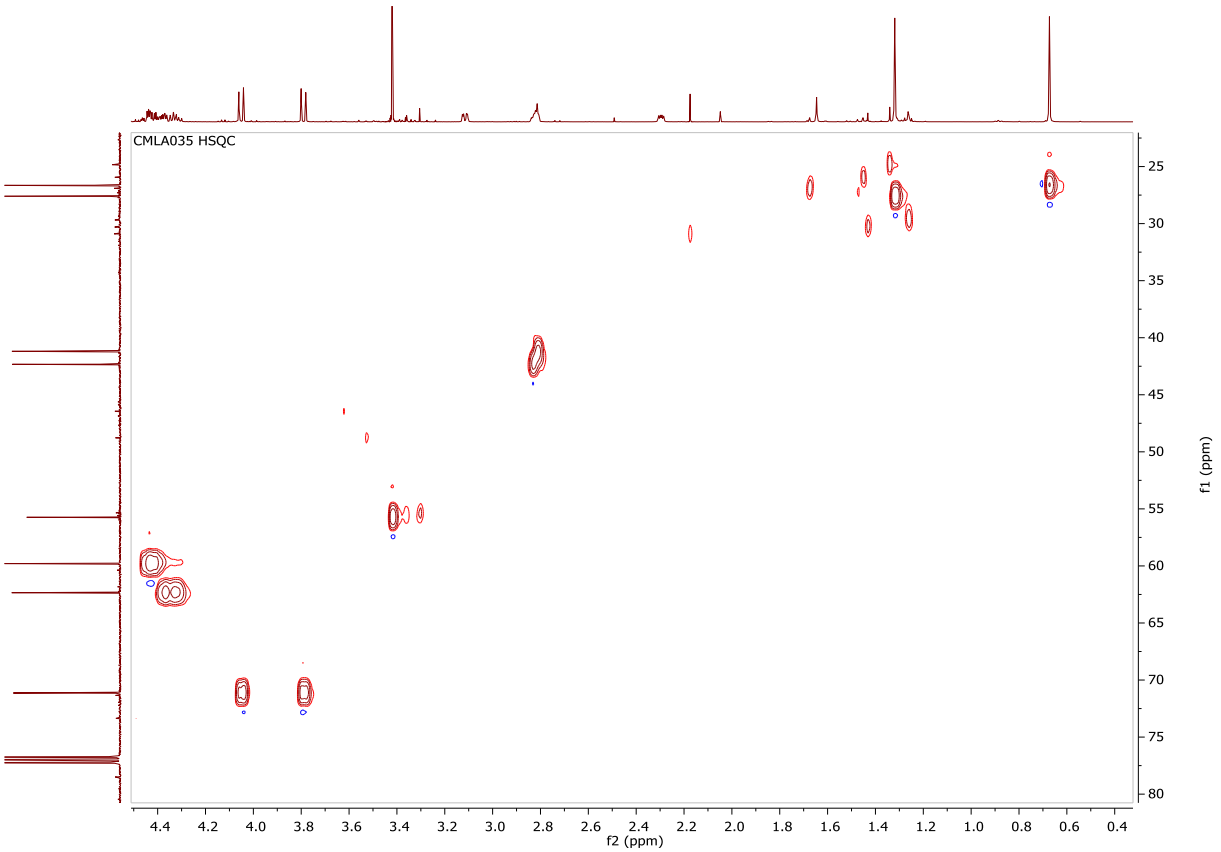
#1 -x+1,y+1/2,-z+1 #2 x+1,y,z #3 x,y-1,z #4 x-1,y,z #5 -x,y-1/2,-z+1 #6 -x,y+1/2,-z+1

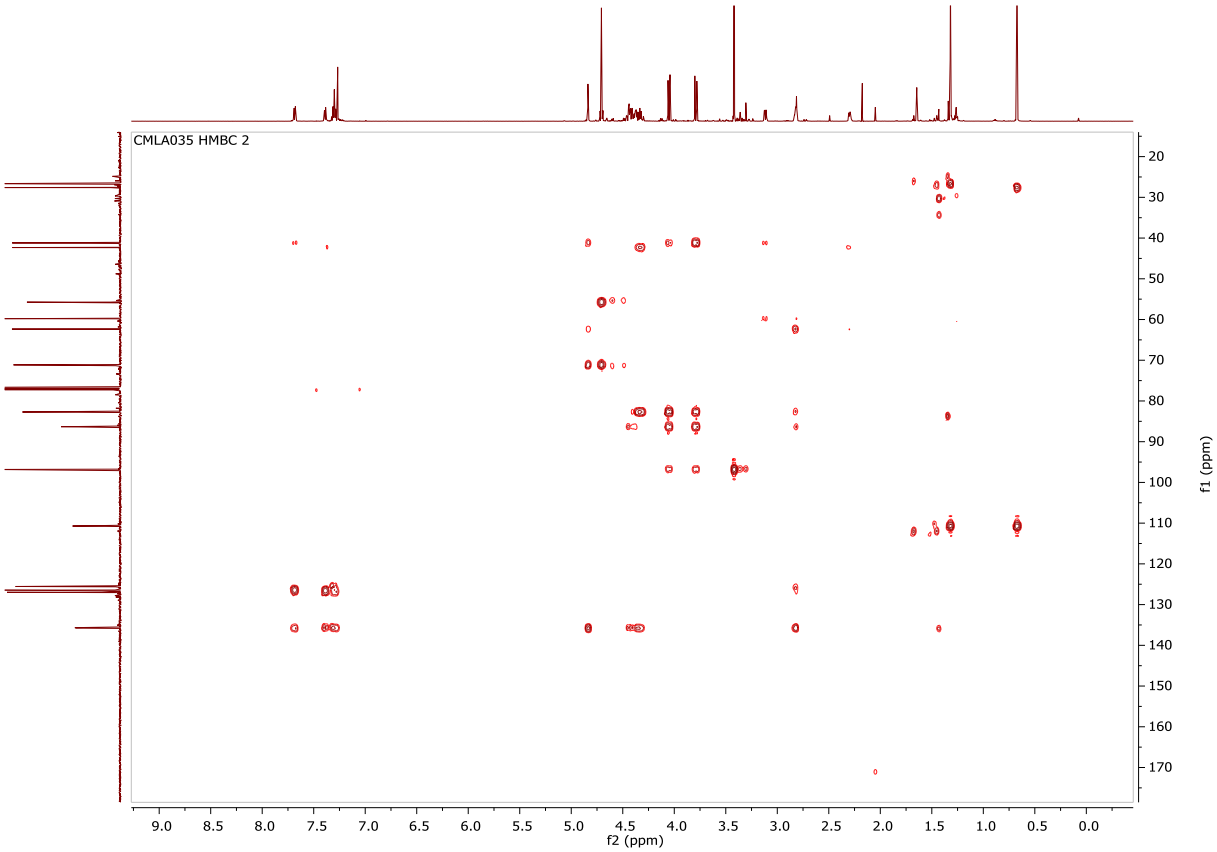
((3a*R*,4*R*,9*S*,9a*R*)-3a-((Methoxymethoxy)methyl)-2,2-dimethyl-3a,4,9,9a-tetrahydronaphtho[2,3-d][1,3]dioxole-4,9-diyl)dimethanol II-70






CMLA035 COSY
f2 (ppm)
f1 (ppm)

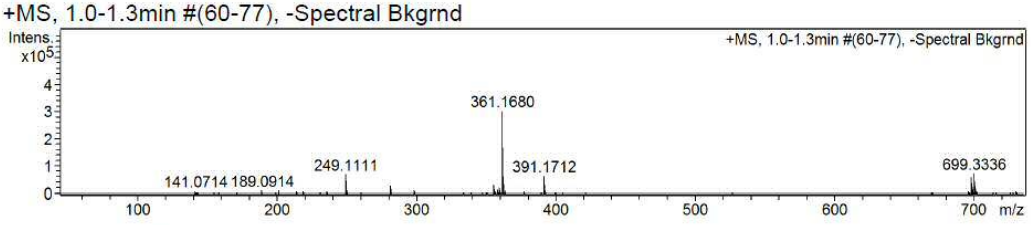

CMLA035 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

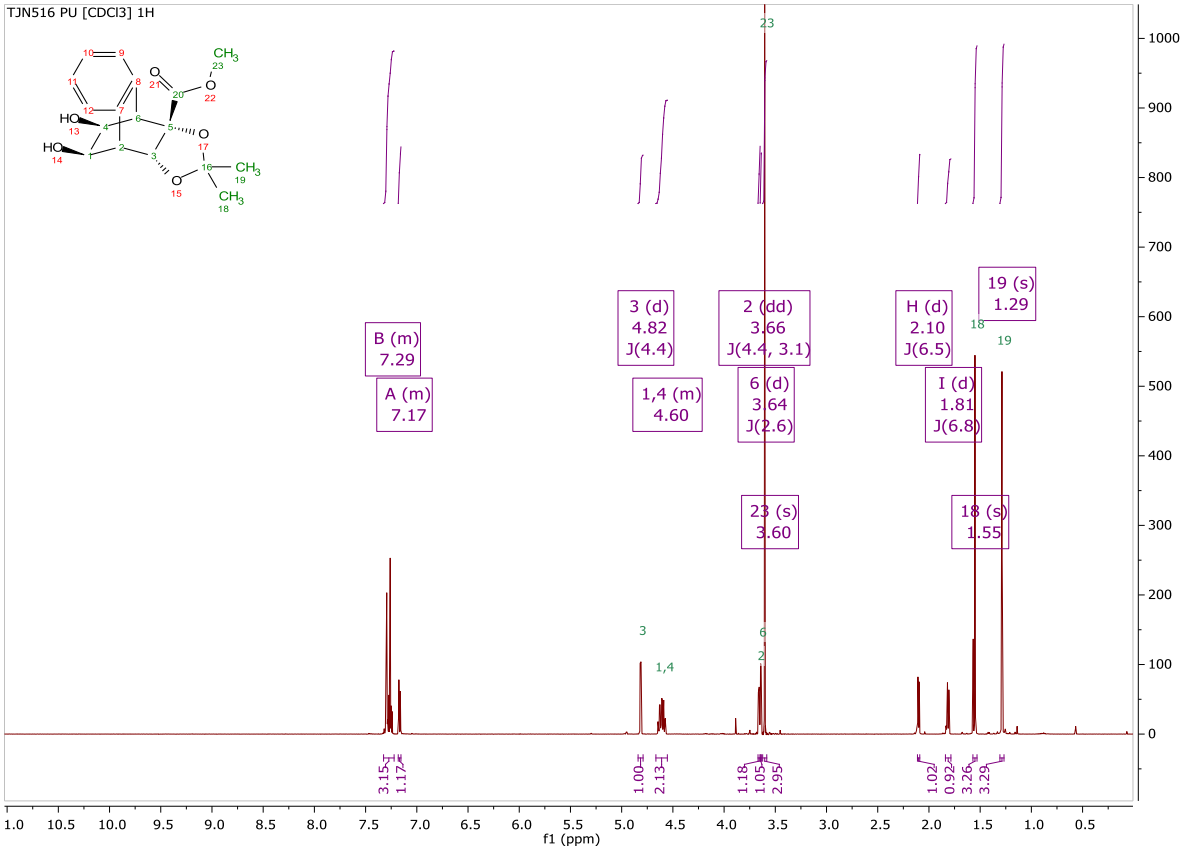
Sample-ID	tn_sel_CMLA035B	Submitter	Toby Nash
Analysis Name	tn_sel_CMLA035B_344215_66_01_48661.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	30/06/2015 15:02:05
Ionisation Mode	positive electrospray (ESI)		

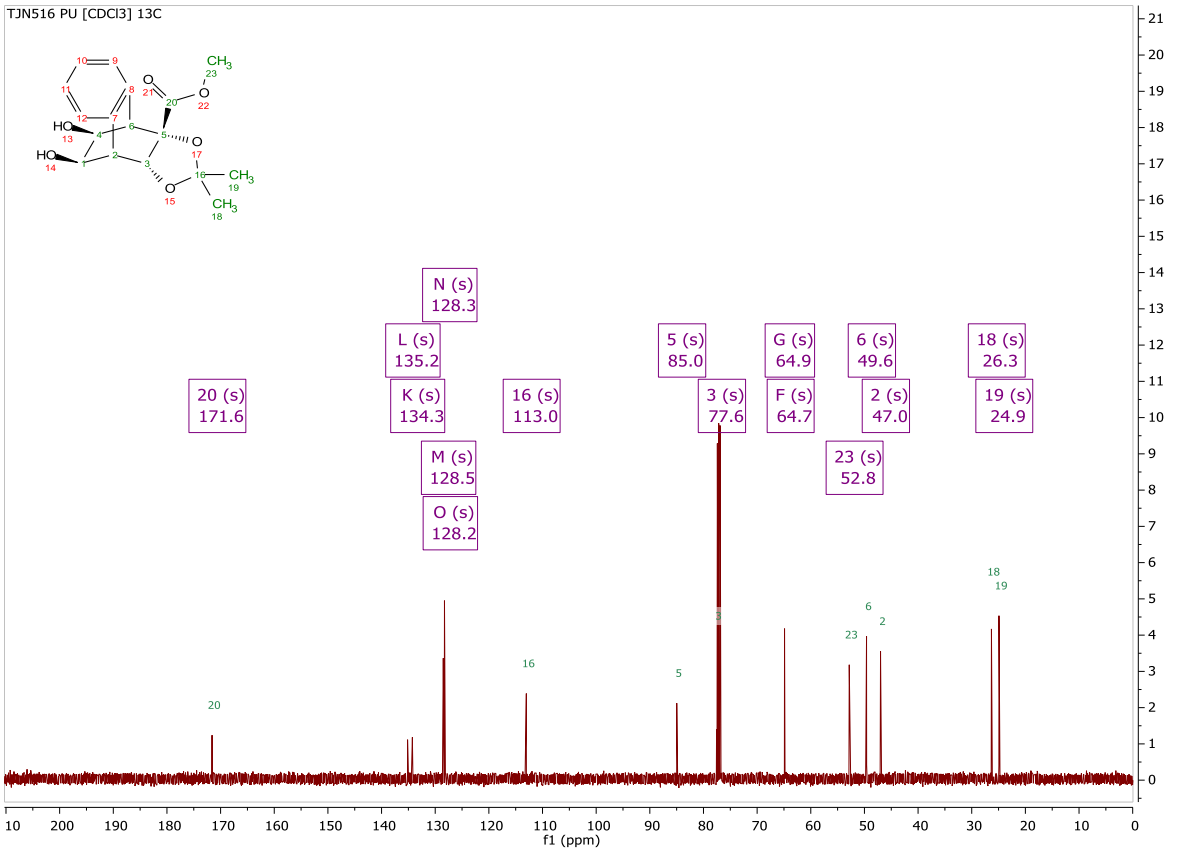
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

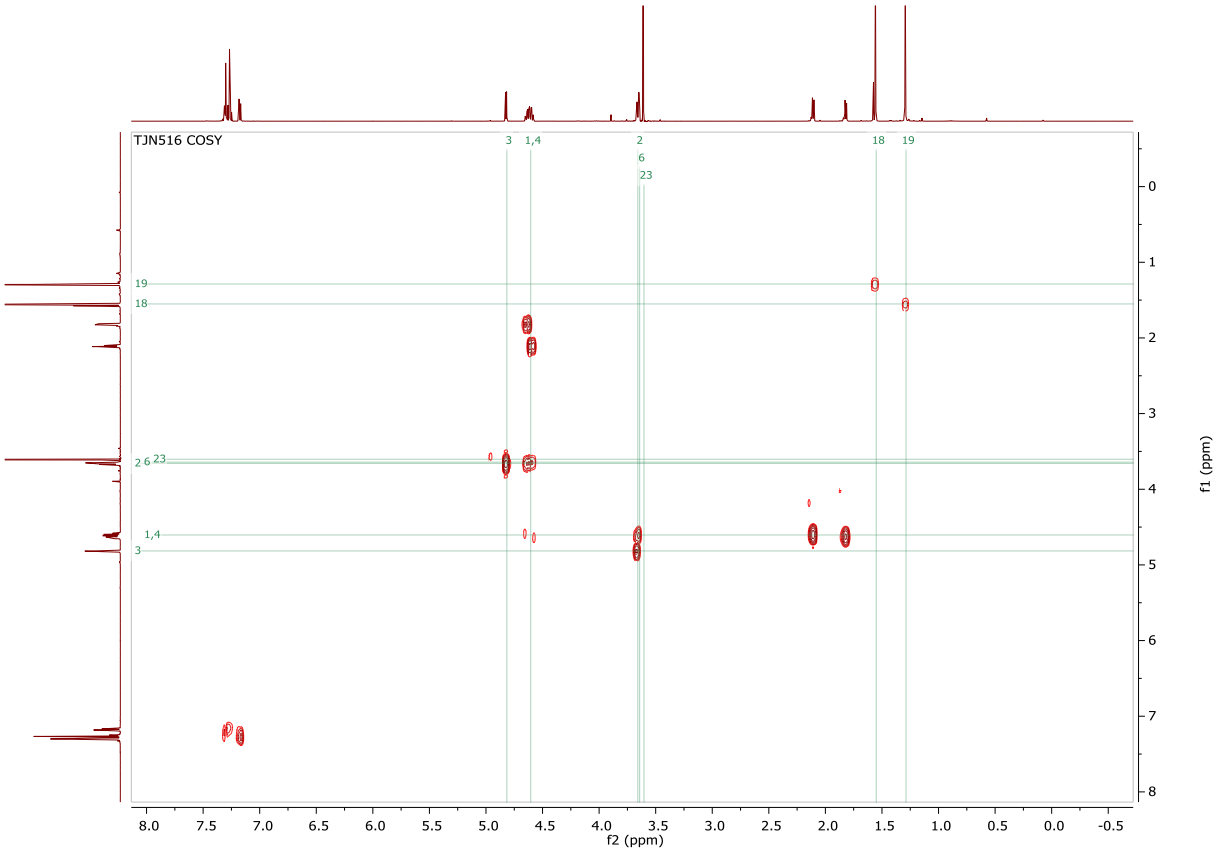


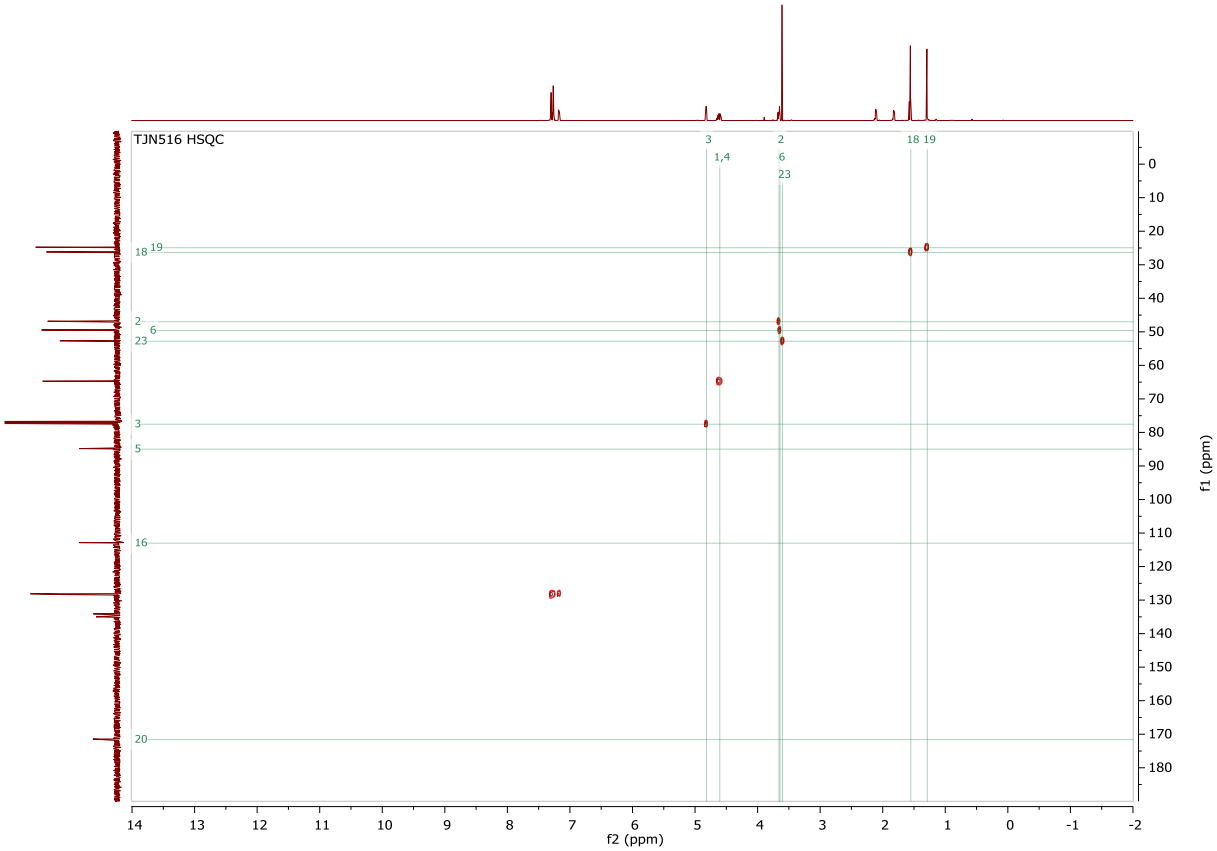
#	m/z	I	I %	Area	S/N
1	249.1111	69843	23.2	3285	4663.5
2	281.1370	27644	9.2	1457	1611.2
3	355.2815	32902	10.9	2252	323.2
4	361.1680	300761	100.0	13617	3280.7
5	362.1647	63620	21.2	4211	707.2
6	391.1712	63884	21.2	4717	1538.9
7	697.3177	60930	20.3	6650	535.9
8	698.3220	25889	8.6	2996	222.4
9	699.3336	72356	24.1	7928	607.6
10	700.3358	29382	9.8	4875	241.2

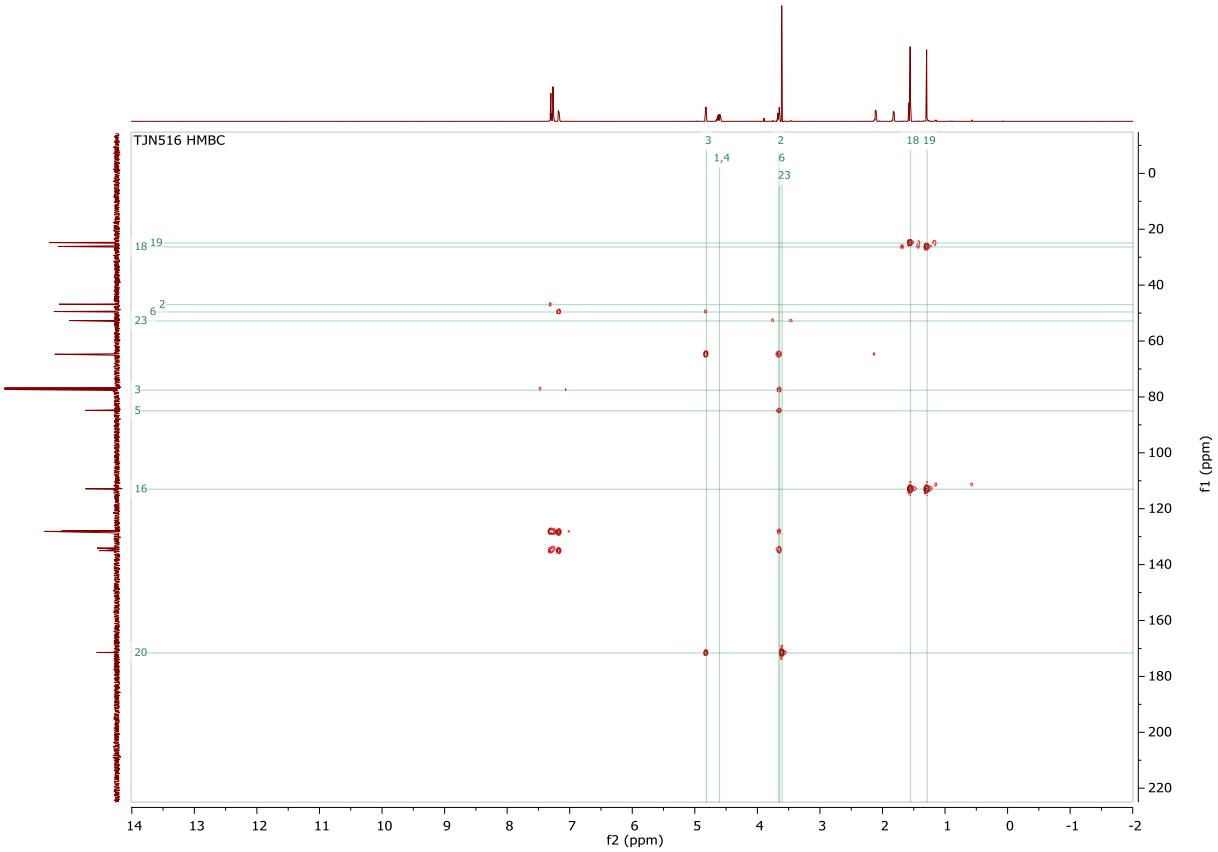
Methyl (3a*R*,4*S*,9*R*,9a*S*,10*S*,11*R*)-10,11-dihydroxy-2,2-dimethyl-4,9-dihydro-4,9-ethanonaphtho[2,3-d][1,3]dioxole-9a(3aH)-carboxylate II-71






TJN516 COSY
3
1,4
2
6
23
18
19
f2 (ppm)
f1 (ppm)

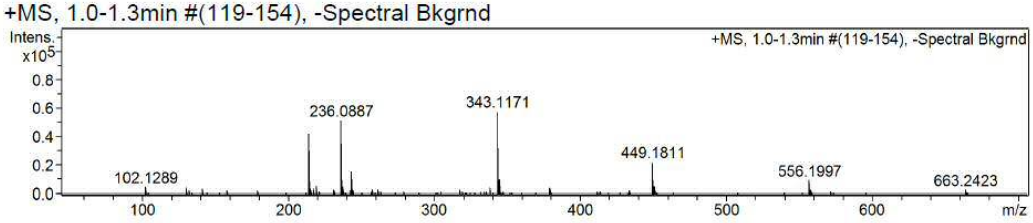

TJN516 HSQC
3
1,4
2
6
23
18
19
20
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

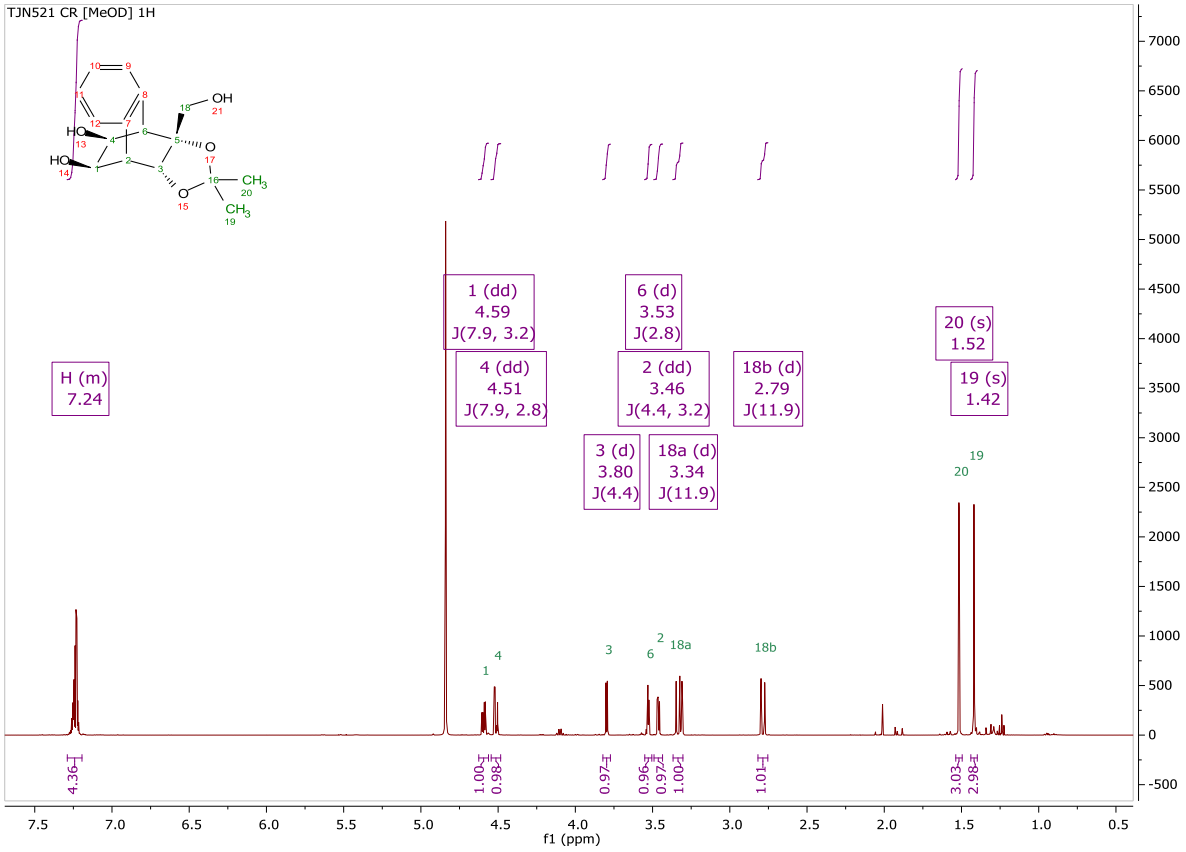
Sample-ID	tn_sel_TJN516	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN516_357332_2_01_63545.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	25/05/2018 10:25:56
Ionisation Mode	positive electrospray (ESI)		

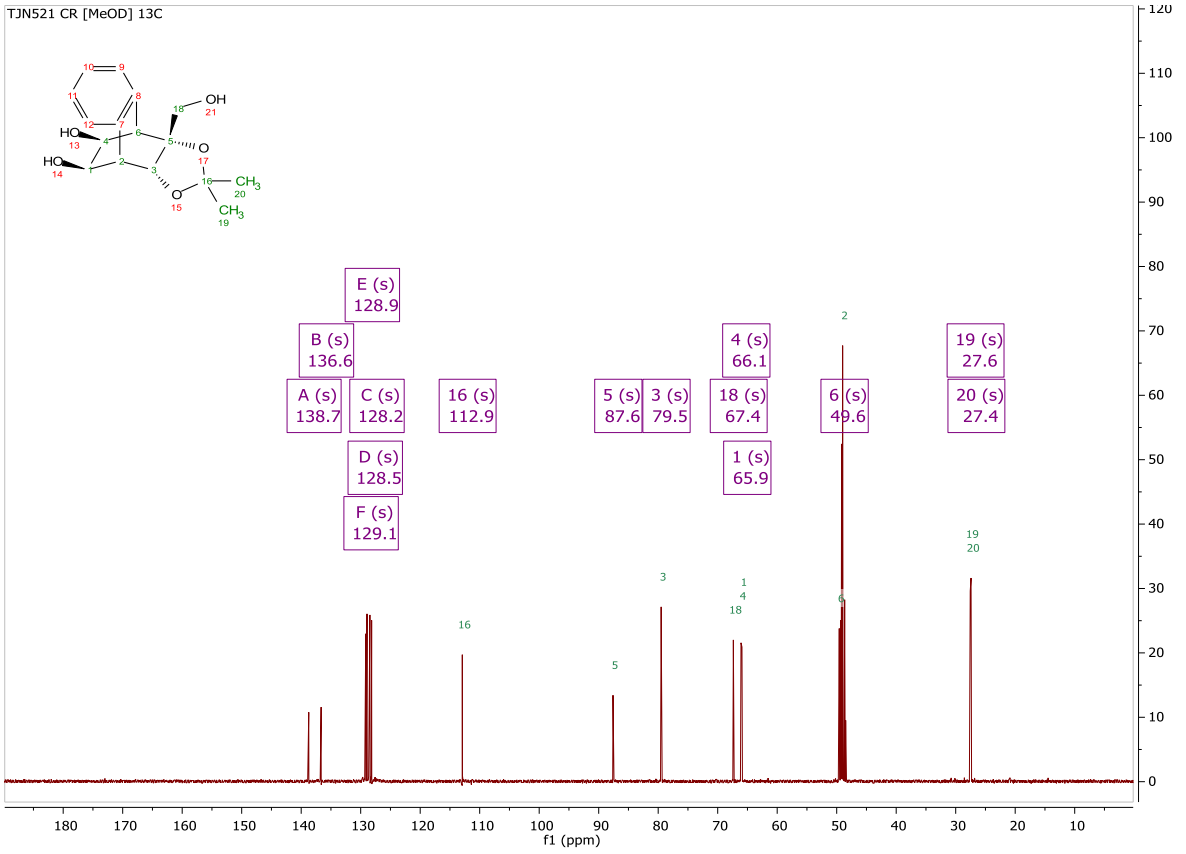
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

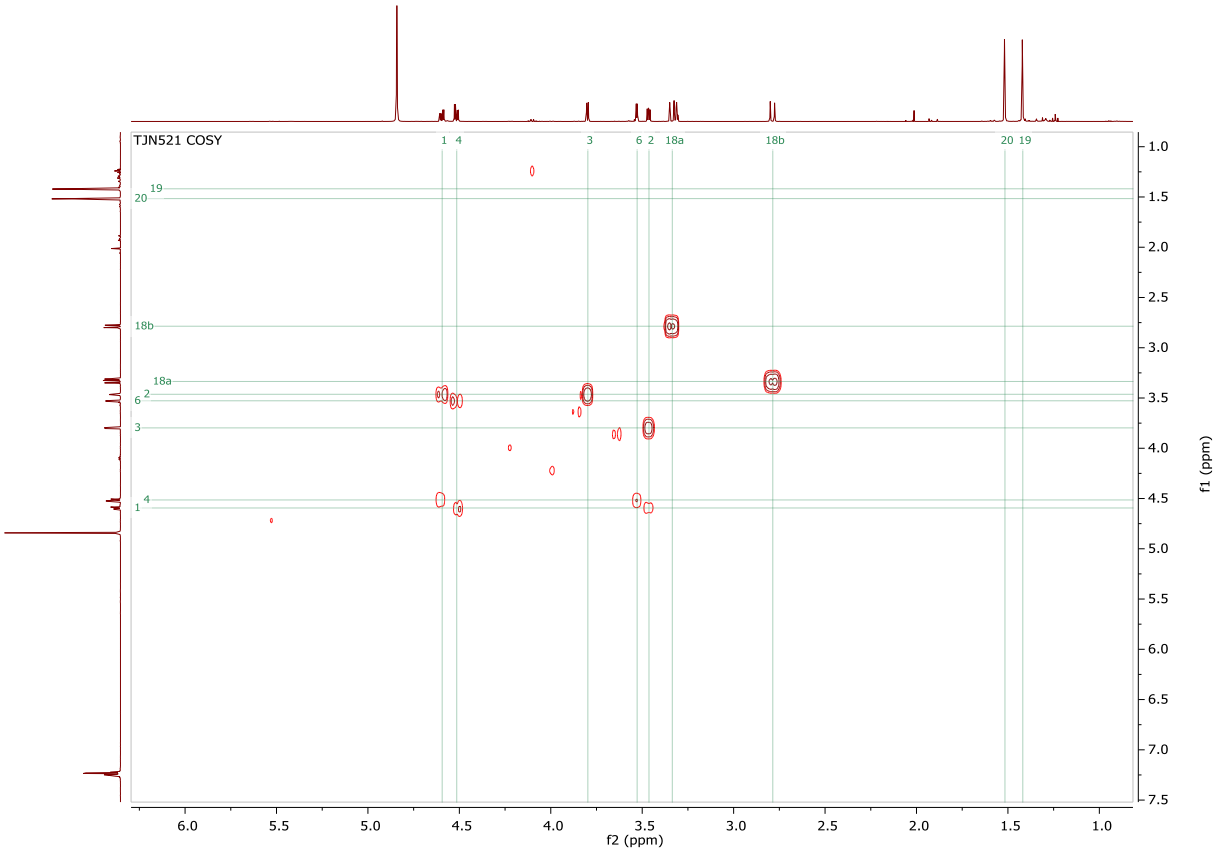


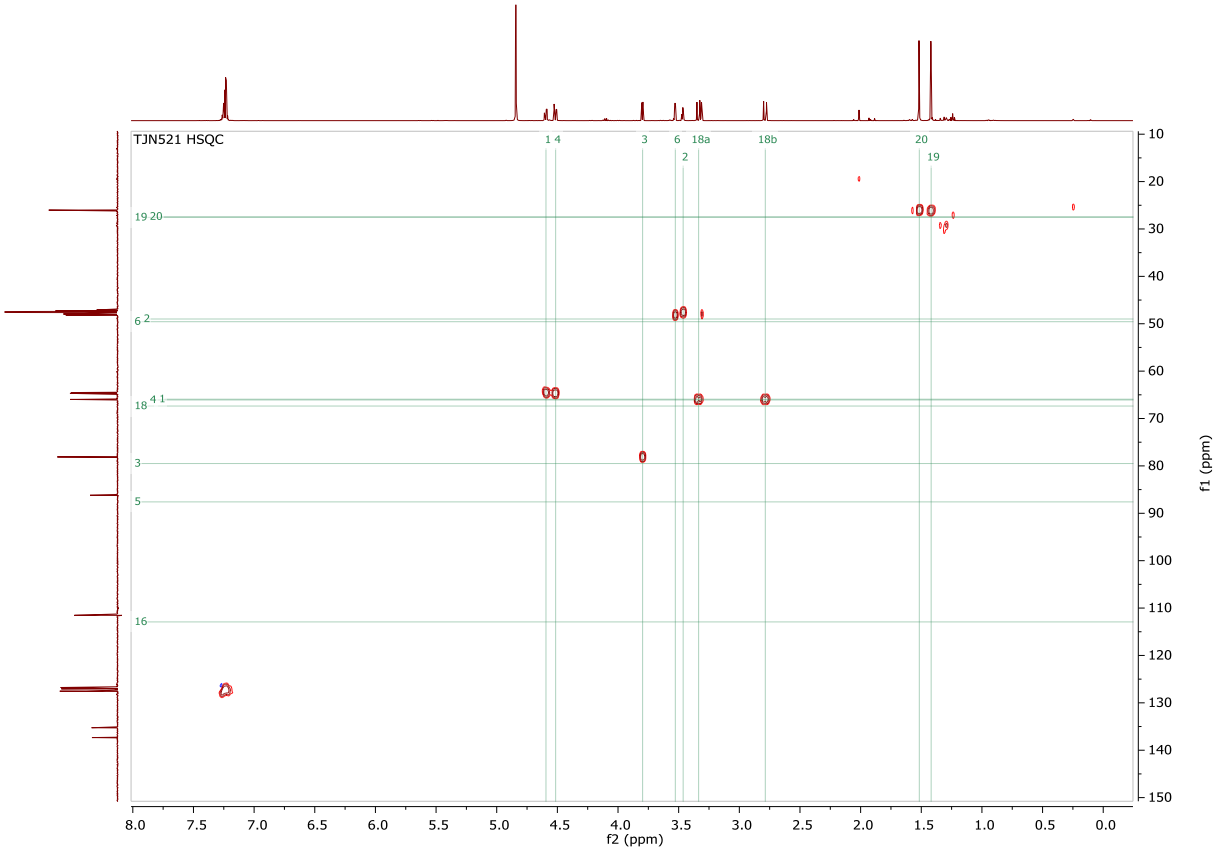
#	m/z	I	I %	Area	S/N
1	214.0956	42235	73.5	837	2482.8
2	219.1376	5889	10.2	208	313.8
3	236.0887	51196	89.1	581	2075.0
4	237.0968	5142	8.9	59	205.5
5	243.1365	15822	27.5	712	584.4
6	343.1171	57467	100.0	3495	1610.9
7	344.1212	10276	17.9	607	292.3
8	449.1811	22351	38.9	801	964.2
9	450.1770	5503	9.6	215	236.1
10	556.1997	9528	16.6	939	520.8

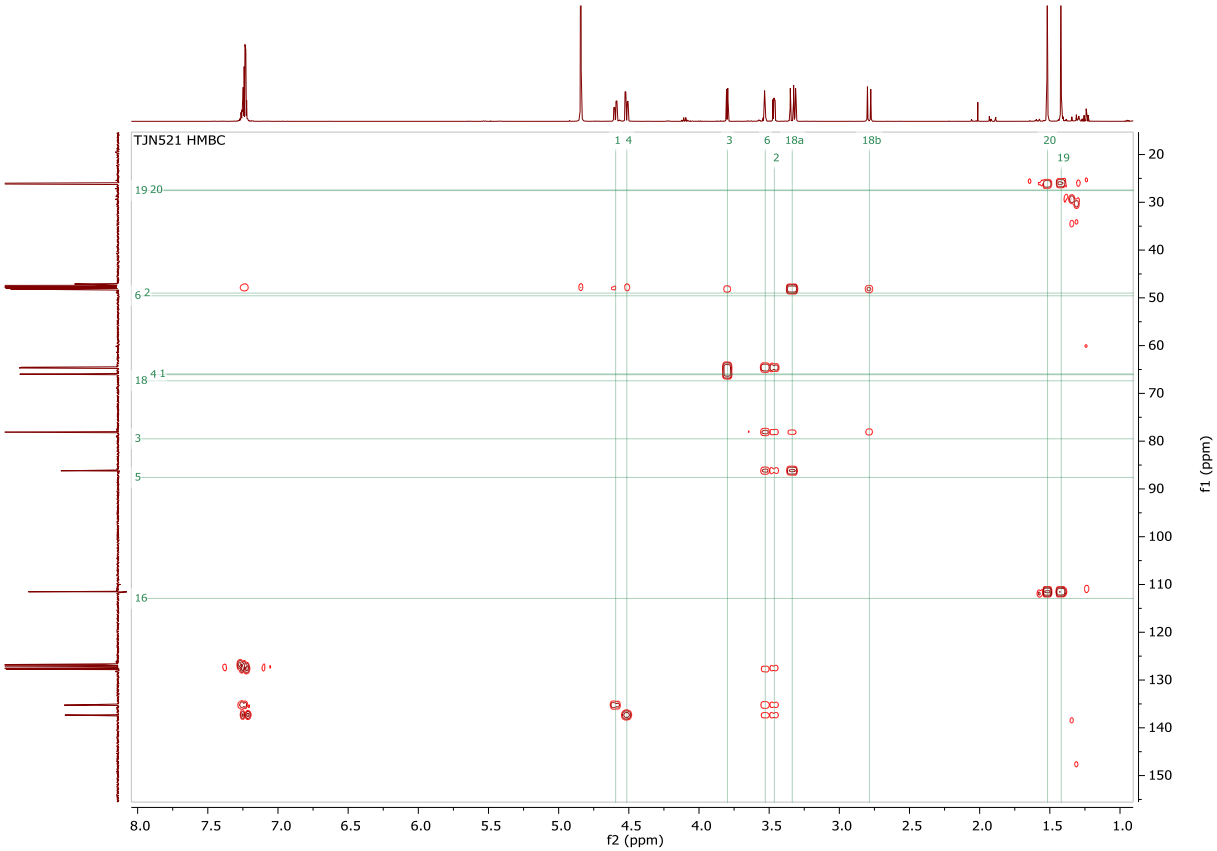
(3a*R*,4*S*,9*R*,9a*R*,10*S*,11*R*)-9a-(Hydroxymethyl)-2,2-dimethyl-3a,4,9,9a-tetrahydro-4,9-ethanonaphtho[2,3-d][1,3]dioxole-10,11-diol II-72






TJN521 COSY
1 4
3
6 2
18a
18b
20 19
f2 (ppm)
f1 (ppm)

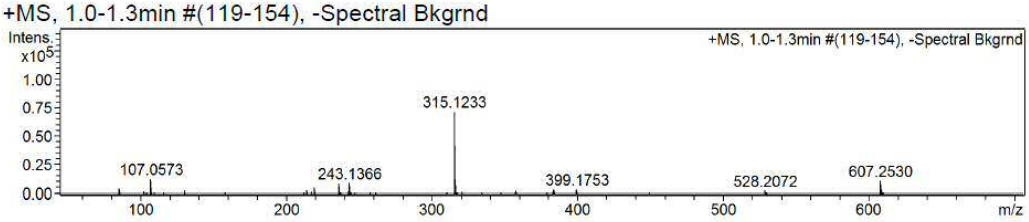

TJN521 HSQC
1 4
3
6
18a
2
18b
20
19
19 20
6 2
18
4 1
3
5
16
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

Sample-ID	tn_sel_TJN521	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN521_357357_32_01_63582.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	29/05/2018 15:31:57
Ionisation Mode	positive electrospray (ESI)		

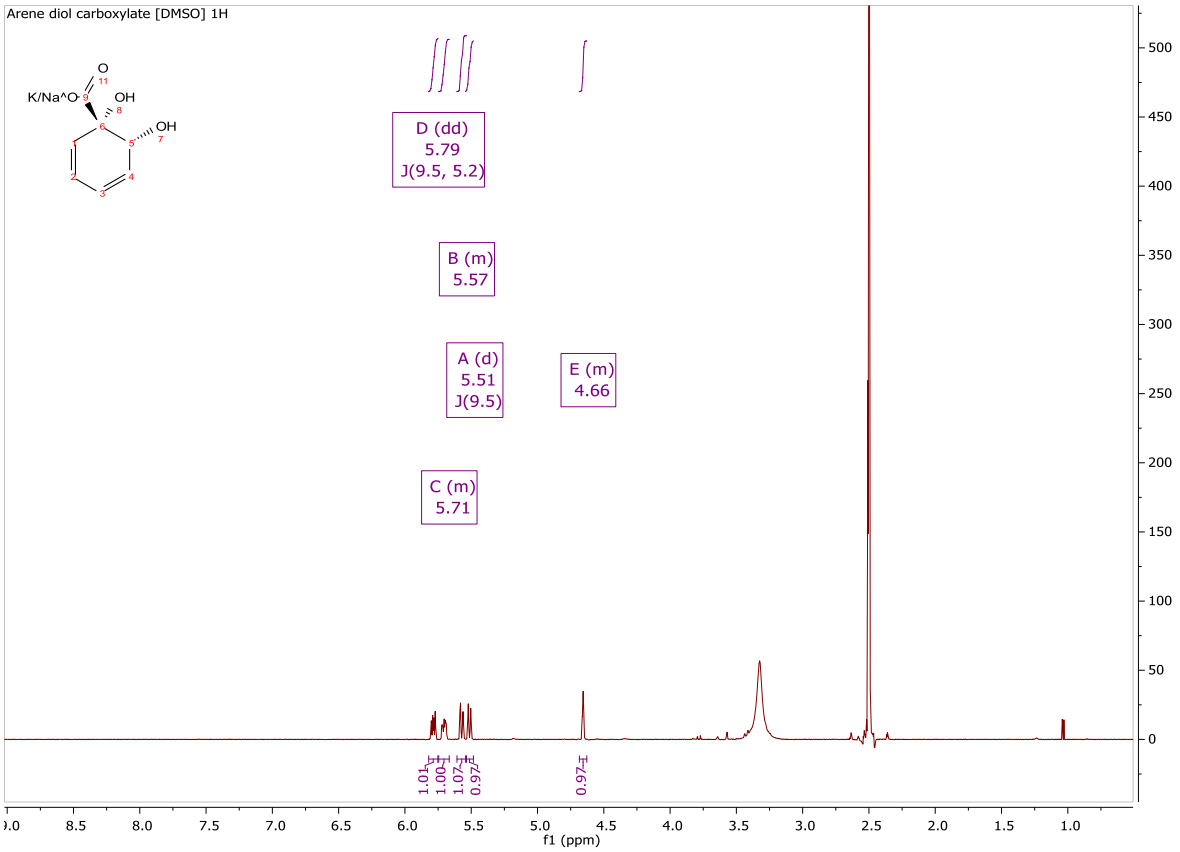
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd



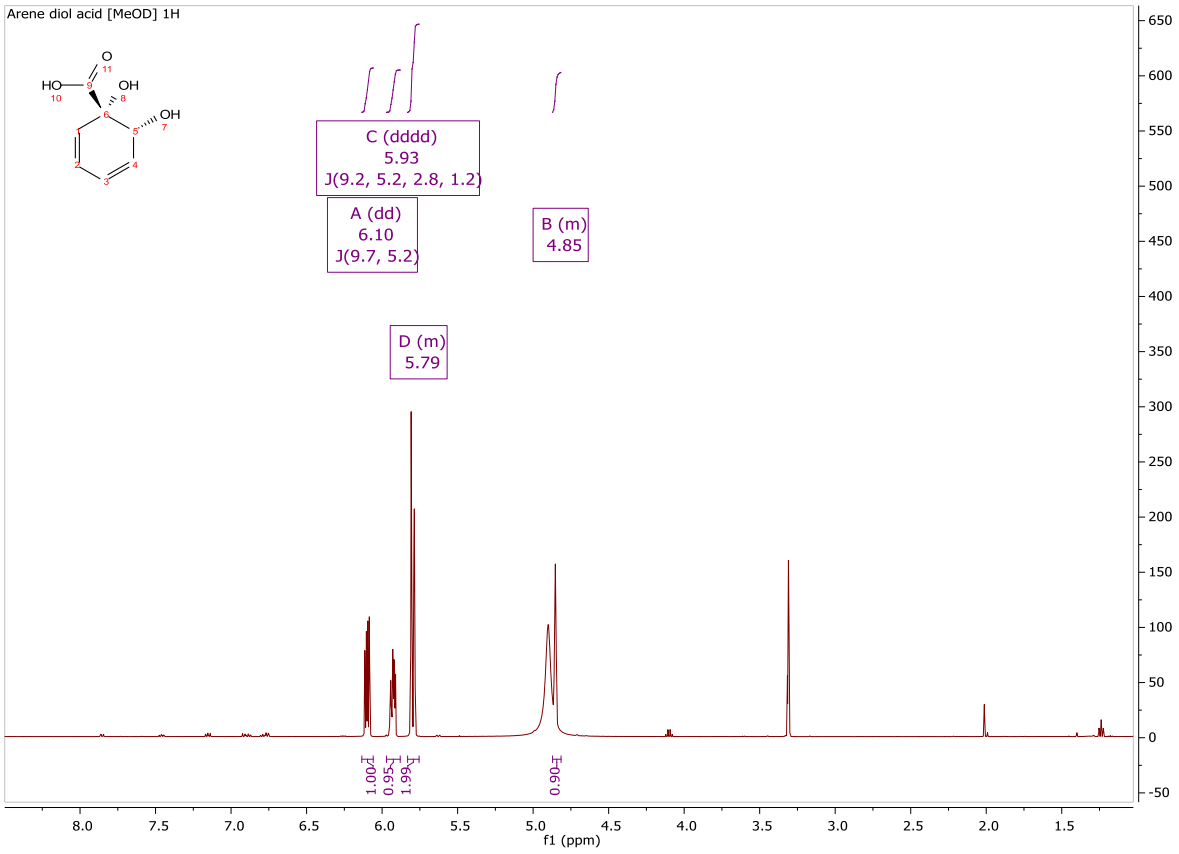
#	m/z	I	I %	Area	S/N
1	85.0589	4297	6.0	61	4673.0
2	107.0573	12927	18.1	90	6810.3
3	219.1373	5510	7.7	204	753.6
4	236.0971	8577	12.0	100	873.3
5	243.1366	9199	12.9	381	848.8
6	315.1233	71494	100.0	3808	4304.1
7	316.1263	12346	17.3	636	727.6
8	399.1753	3969	5.6	248	640.4
9	607.2530	11139	15.6	1360	2741.3
10	608.2552	3641	5.1	431	911.6

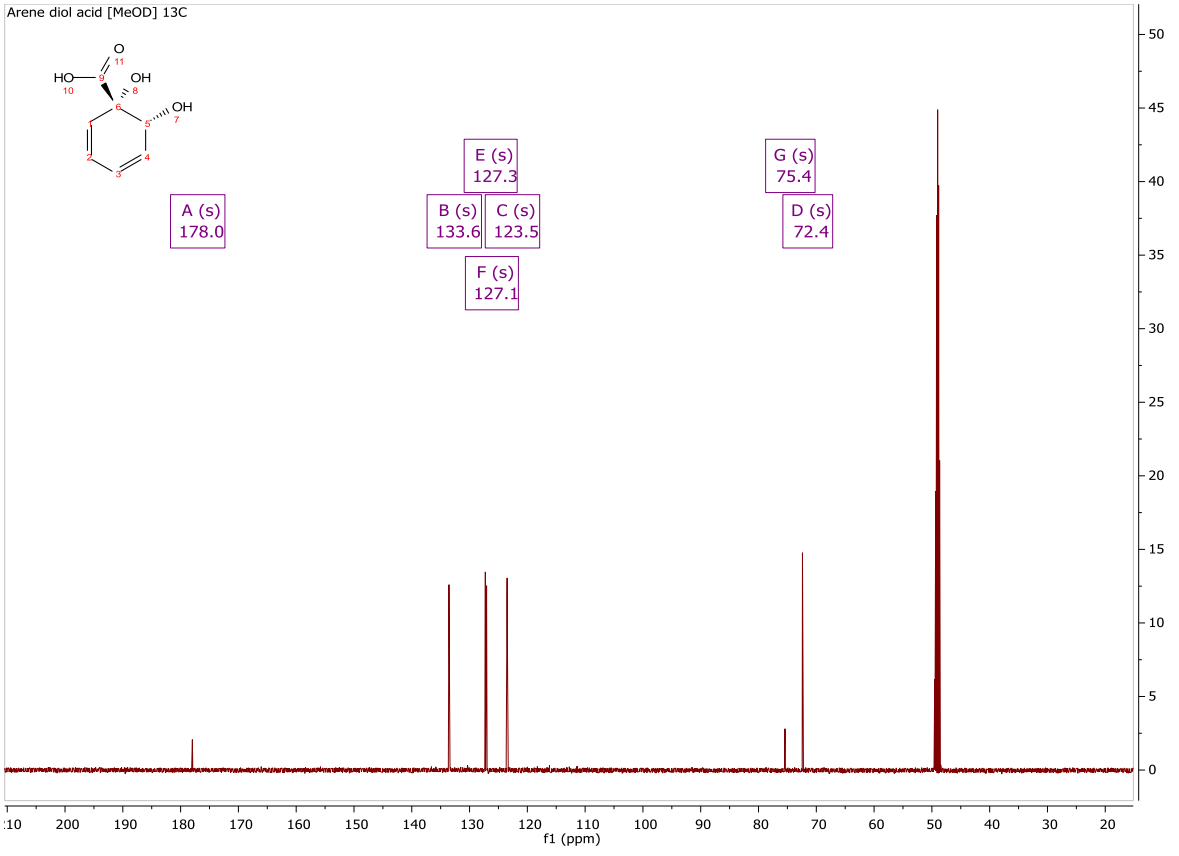
Synthesis and testing of a novel epoxidation catalyst: data

Potassium/sodium (1*S*,6*R*)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate III-20

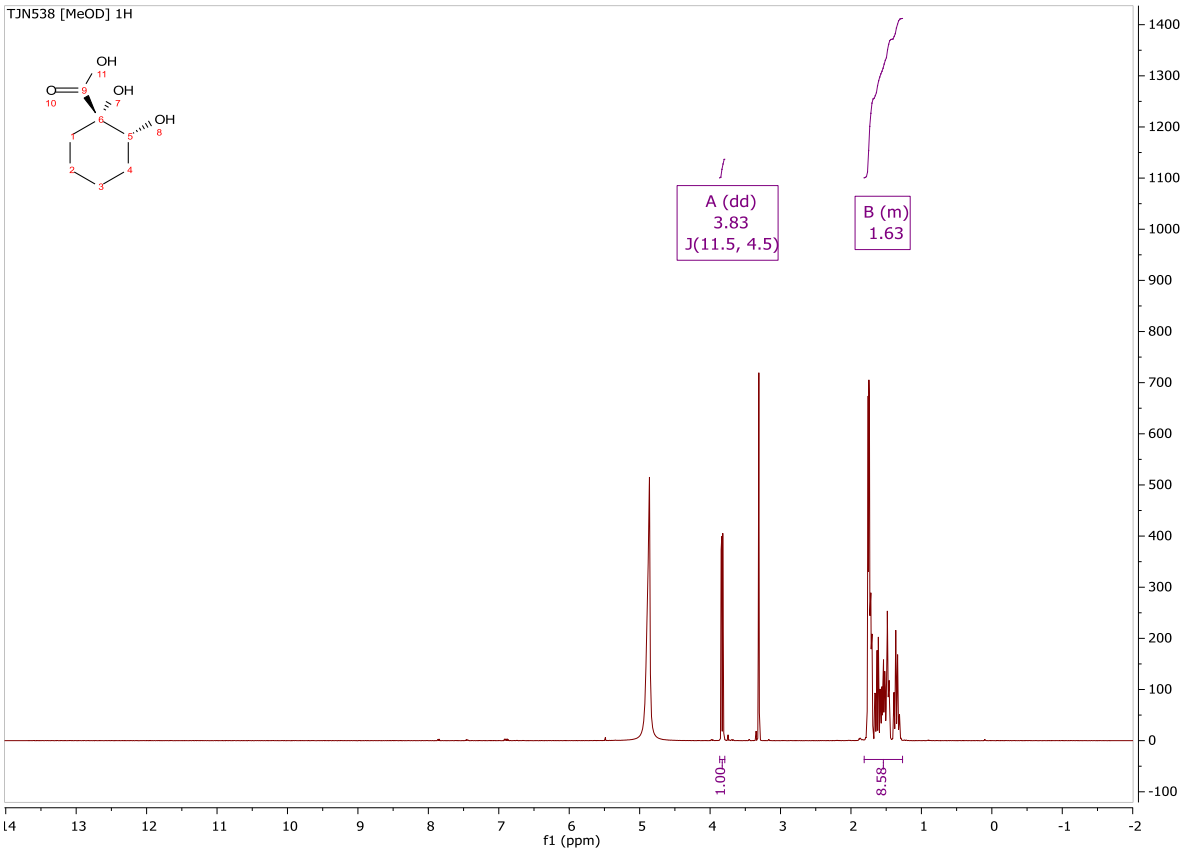


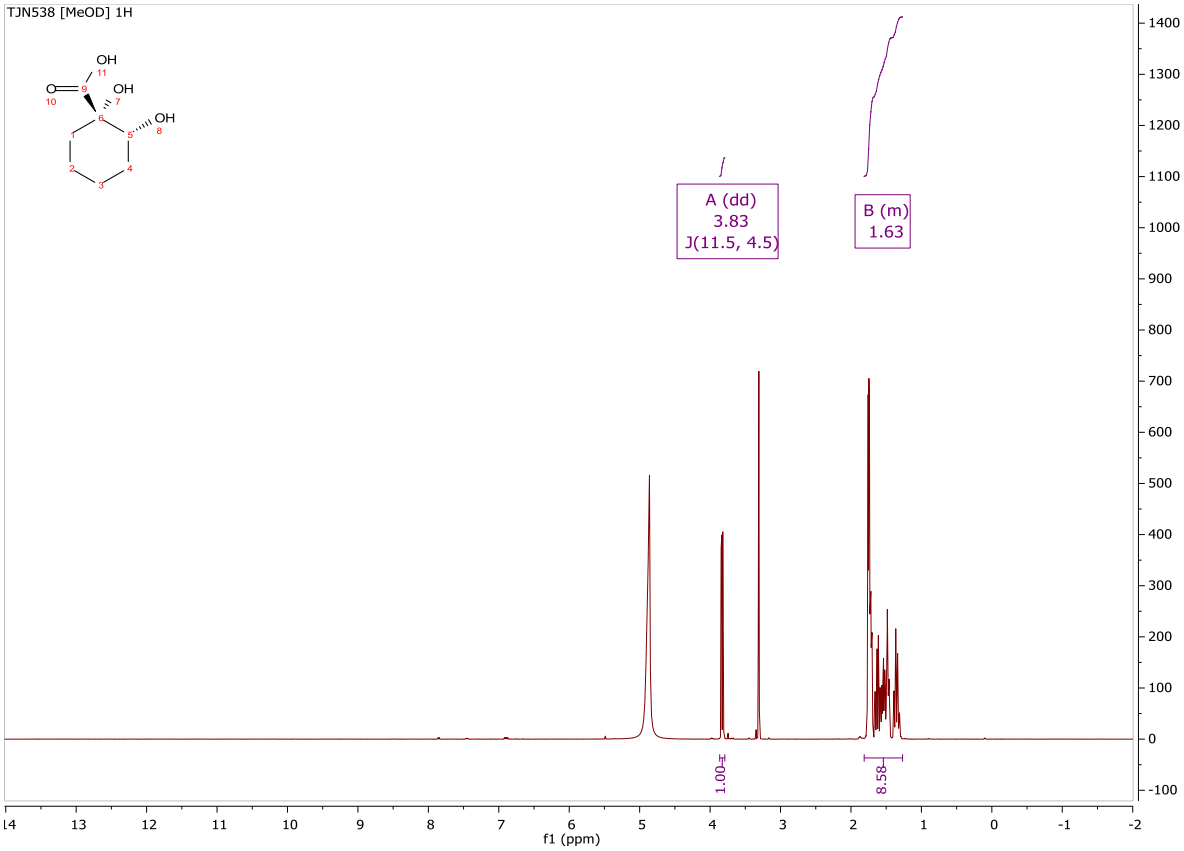
(1*S*,6*R*)-1,6-Dihydroxycyclohexa-2,4-diene-1-carboxylic acid III-21



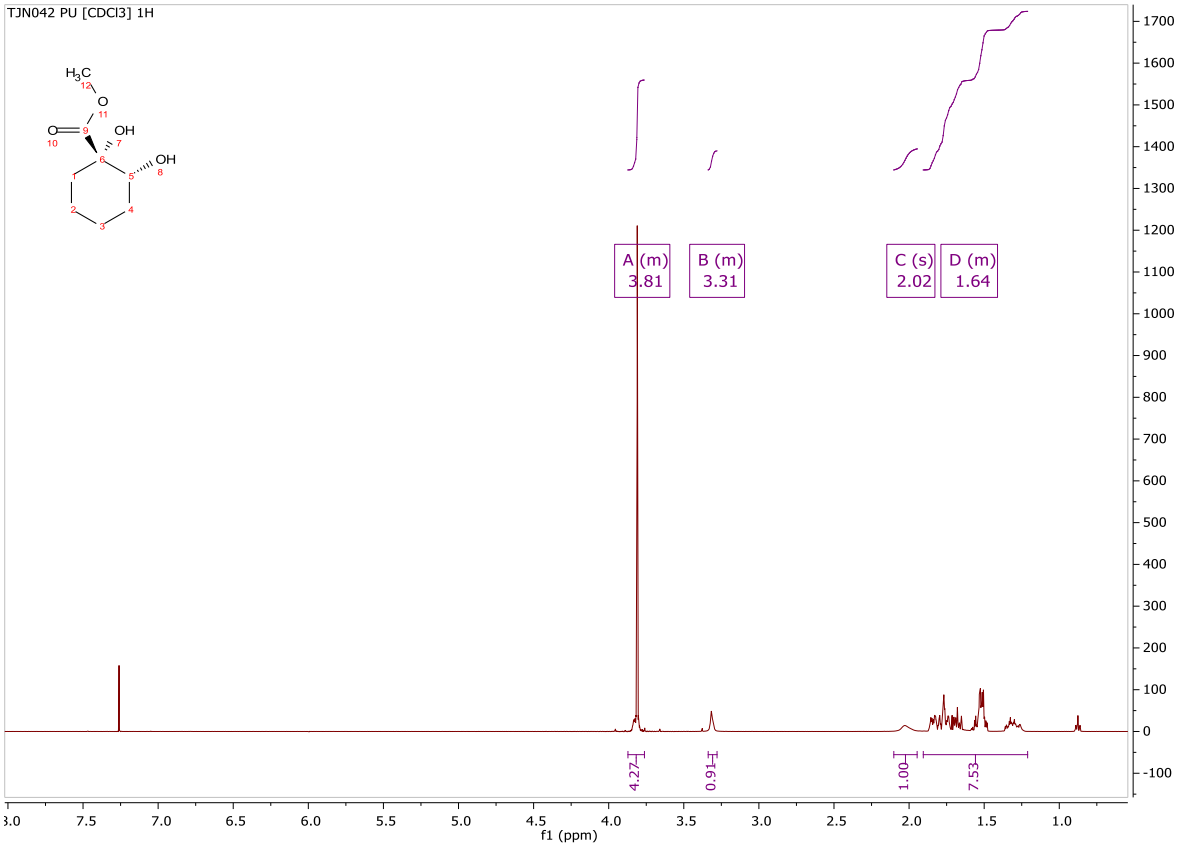


(1*S*,2*R*)-1,2-Dihydroxycyclohexane-1-carboxylic acid III-22





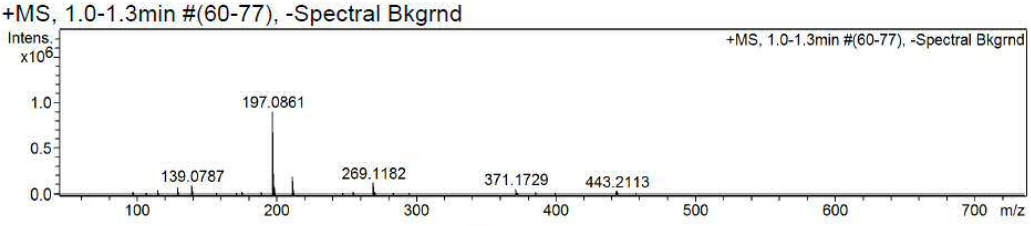
Methyl (1*S*,2*R*)-1,2-dihydroxycyclohexane-1-carboxylate III-23



Confirmation of Expected Formula

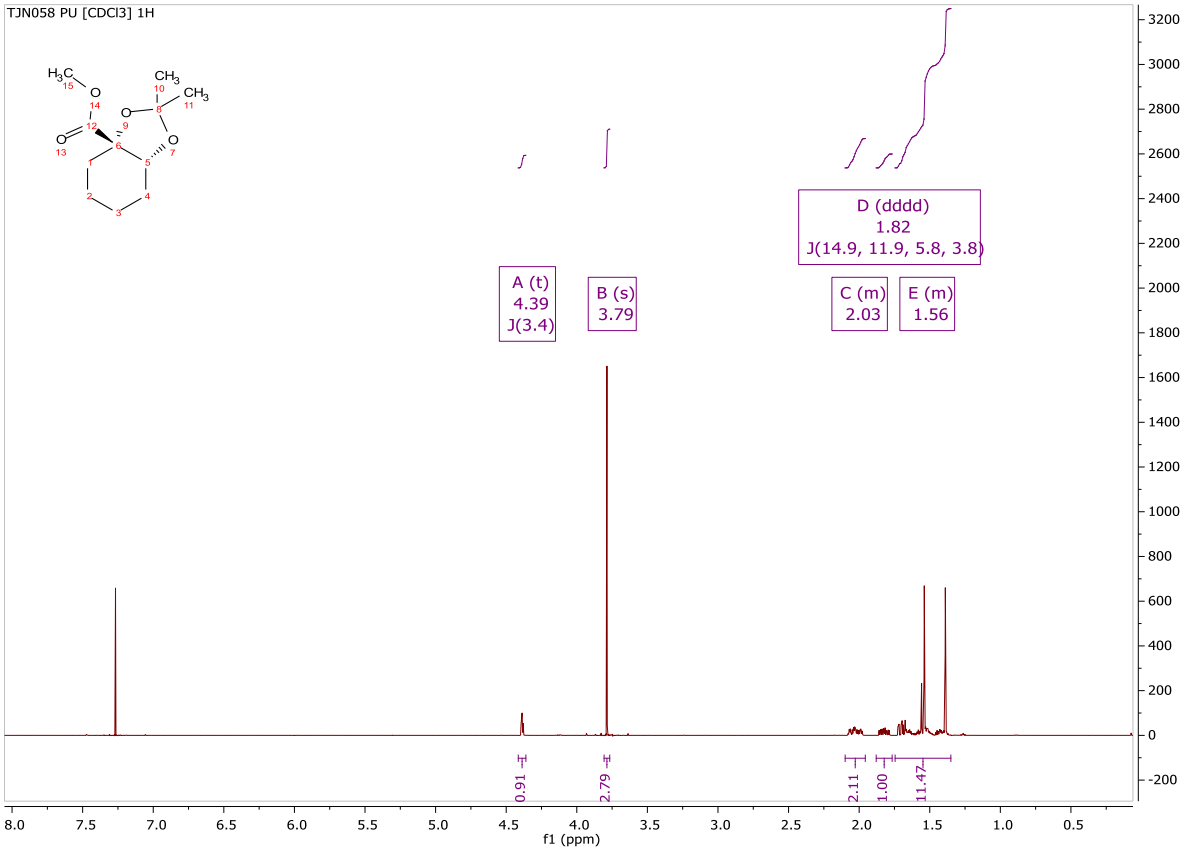
Sample-ID	tn_sel_92	Submitter	Toby Nash
Analysis Name	tn_sel_92_344680_35_01_49194.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	18/08/2015 10:13:46
Ionisation Mode	positive electrospray (ESI)		

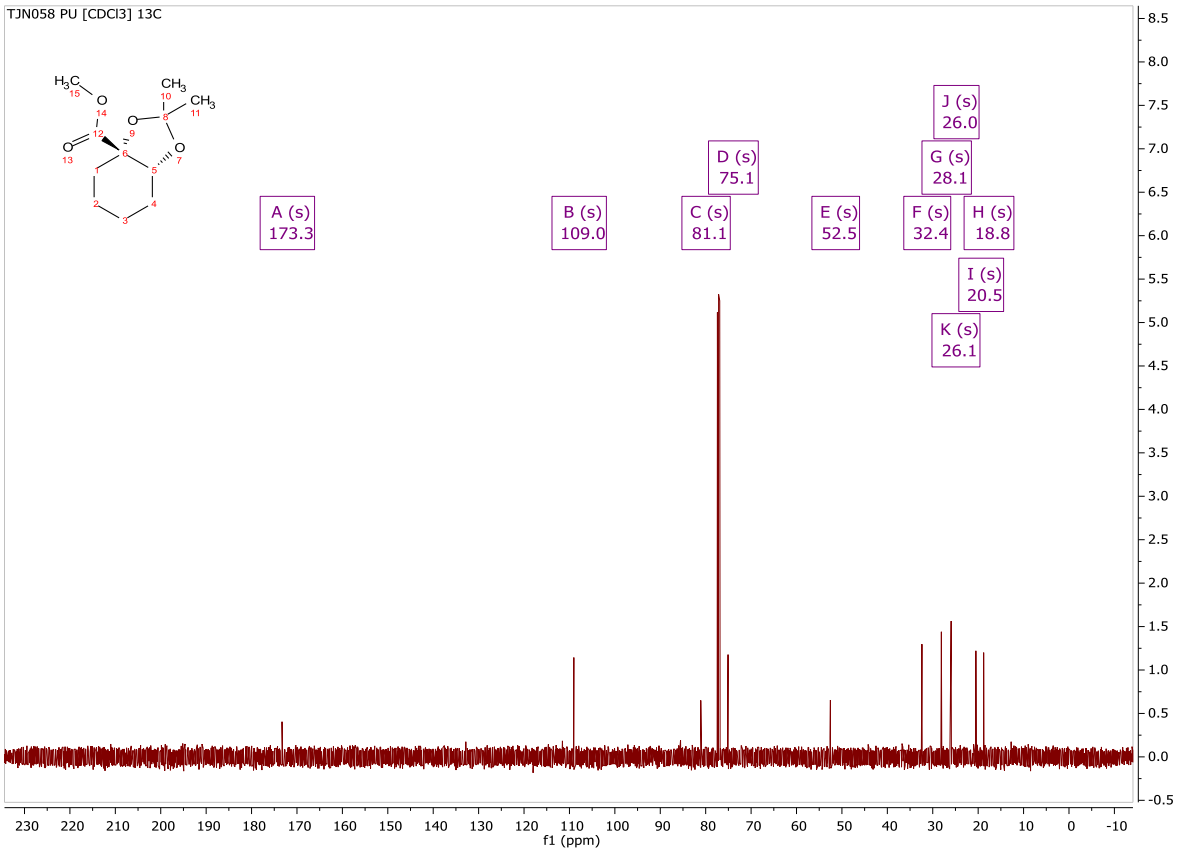
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



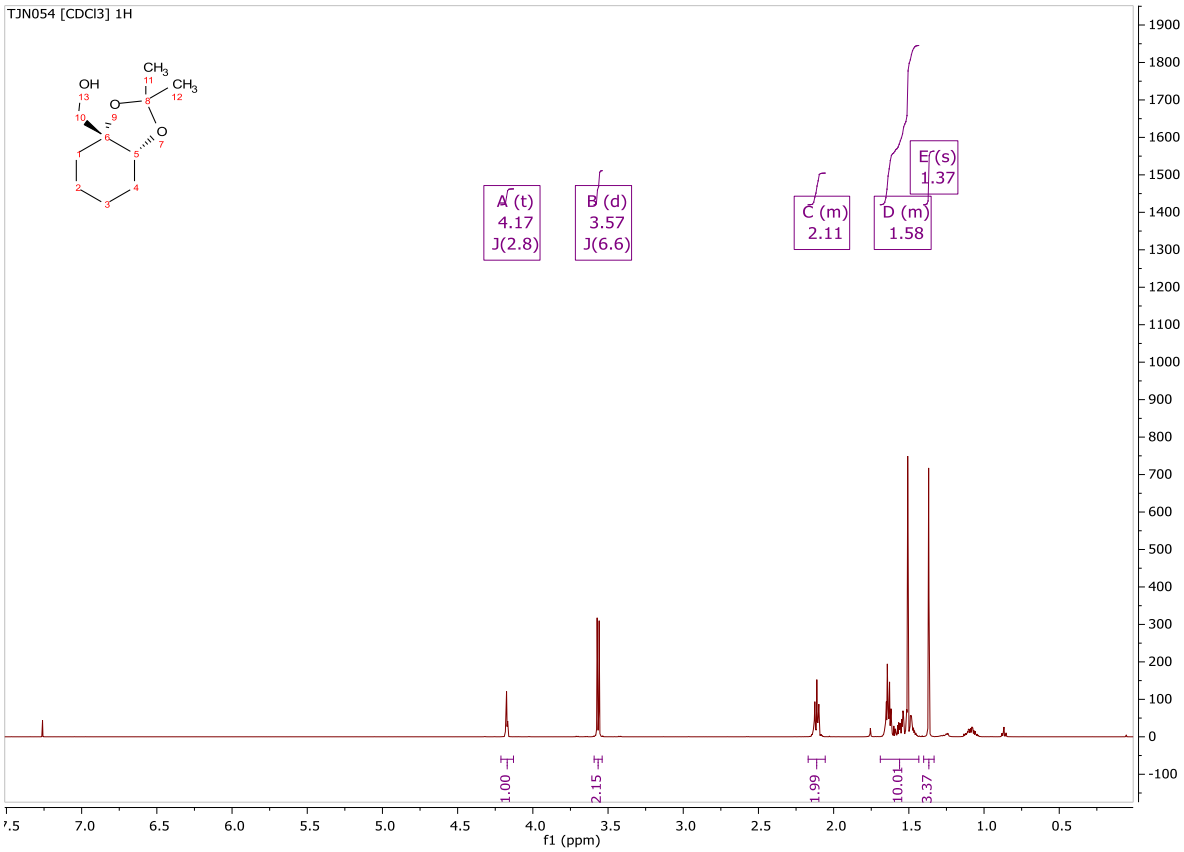
#	m/z	I	I %	Area	S/N
1	97.0655	29221	3.3	576	6256.4
2	115.0777	45600	5.1	977	6126.4
3	129.0936	74679	8.3	2029	8129.5
4	139.0787	91844	10.2	2600	8807.7
5	197.0861	898260	100.0	21377	13731.5
6	198.0811	71300	7.9	2526	1067.1
7	211.0958	192572	21.4	7496	2604.1
8	269.1182	124742	13.9	5953	3311.9
9	371.1729	57794	6.4	3969	1496.1
10	443.2113	32445	3.6	2922	649.5

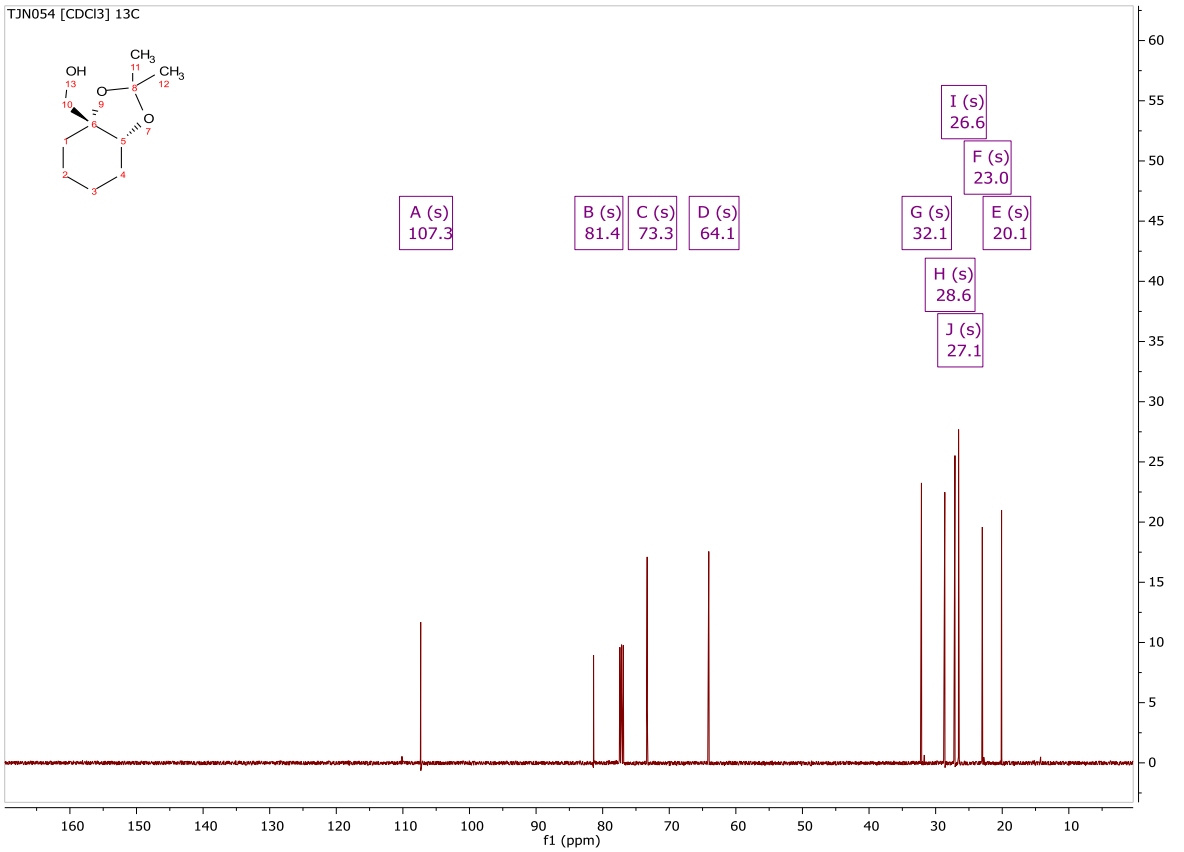
Methyl (3a*S*,7a*R*)-2,2-dimethyltetrahydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate III-24





((3a*R*,7a*R*)-2,2-Dimethyltetrahydrobenzo[d][1,3]dioxol-3a(4H)-yl)methanol III-32

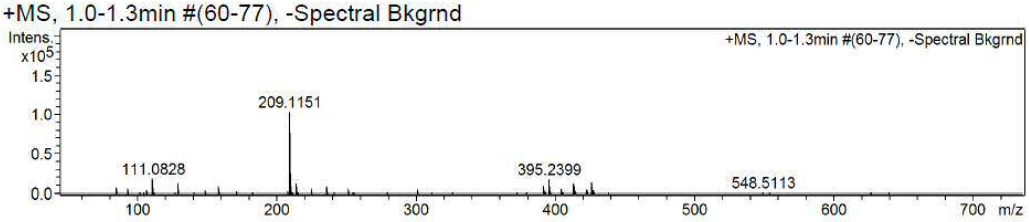




Confirmation of Expected Formula

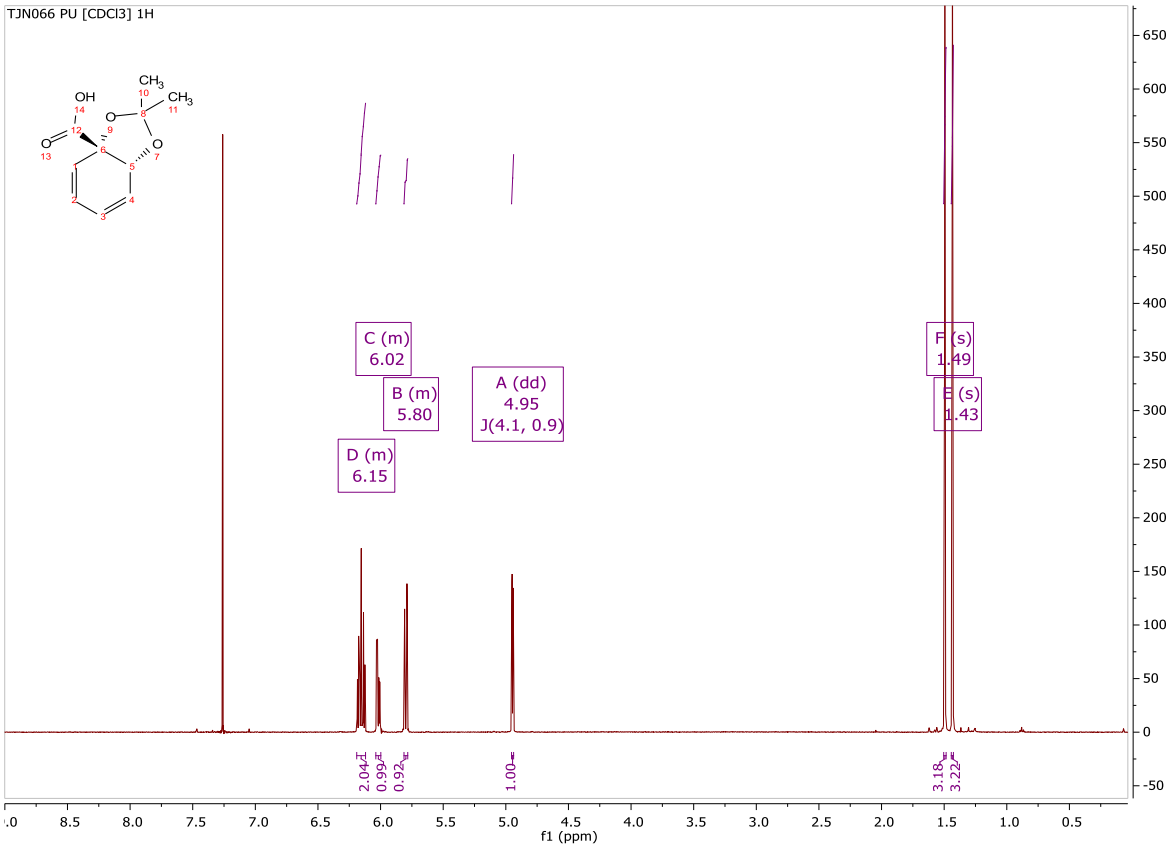
Sample-ID	tn_sel_067	Submitter	Toby Nash
Analysis Name	tn_sel_067_343961_18_01_48382.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	04/06/2015 15:00:54
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	111.0828	19384	18.7	477	4619.9
2	129.0927	13892	13.4	390	3197.0
3	158.0402	9249	8.9	126	2235.8
4	209.1151	103769	100.0	4137	5157.7
5	210.1188	11814	11.4	518	594.6
6	214.1077	11987	11.6	285	635.1
7	391.2832	9725	9.4	832	540.1
8	395.2399	18604	17.9	1620	994.2
9	413.2702	11817	11.4	917	538.6
10	426.1645	15119	14.6	1360	623.5

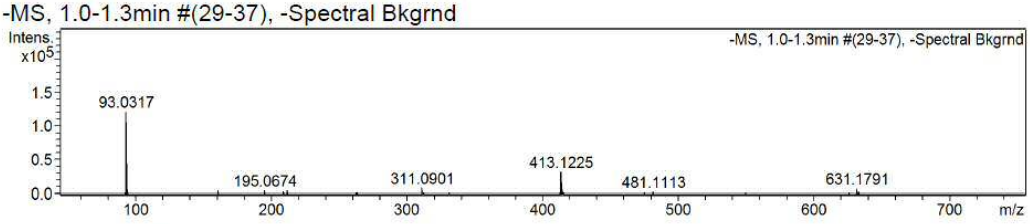
(3a*S*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylic acid III-33



Confirmation of Expected Formula

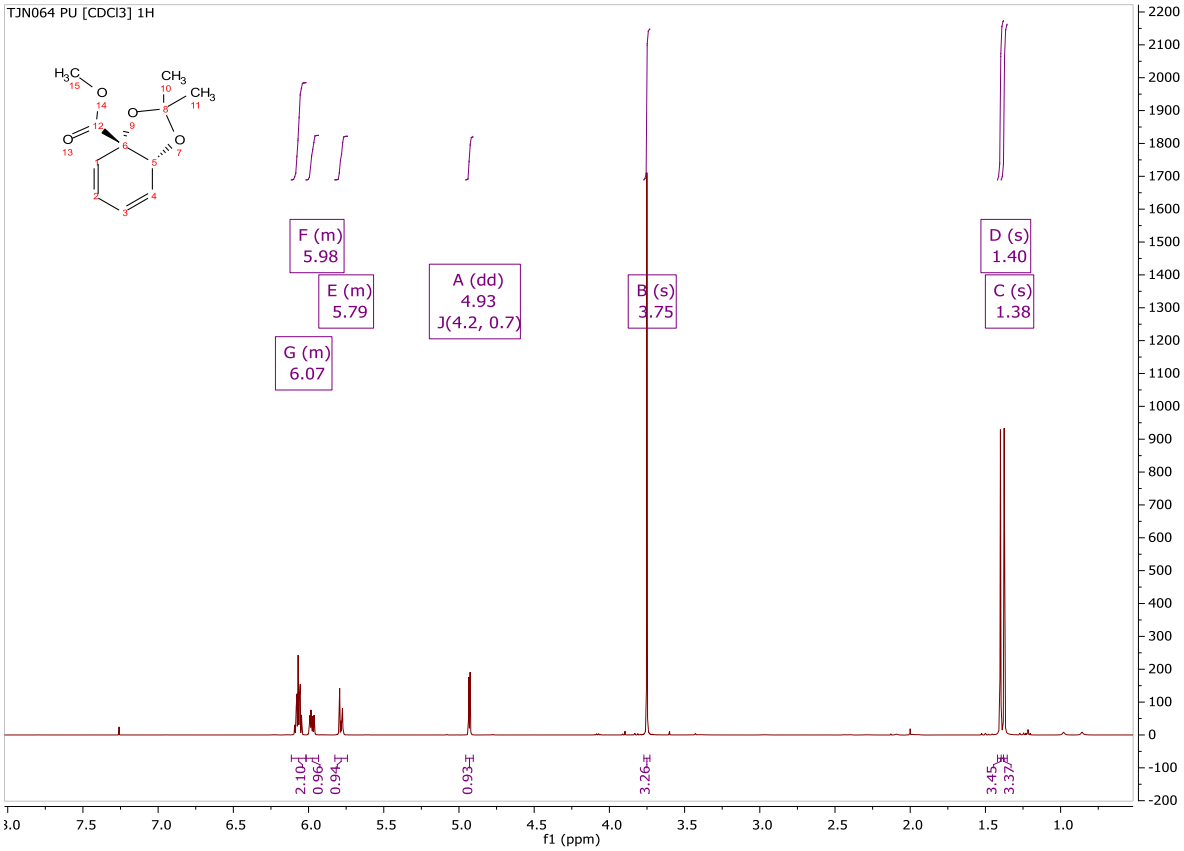
Sample-ID	tn_sel_066	Submitter	Toby Nash
Analysis Name	tn_sel_066_343936_74_01_48351.d	Supervisor	Simon Lewis
Method used	Confirm Formula Negative 50to500 loop inj.m	Acquisition Date	02/06/2015 12:45:57
Ionisation Mode	negative electrospray (ESI)		

-MS, 1.0-1.3min #(29-37), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	93.0317	121185	100.0	2778	17623.1
2	94.0353	8474	7.0	189	1246.7
3	161.0240	4793	4.0	130	1528.0
4	195.0674	5368	4.4	184	1382.3
5	209.0590	3122	2.6	120	734.2
6	212.0776	5011	4.1	74	1182.5
7	311.0901	8832	7.3	482	1862.9
8	413.1225	32163	26.5	2184	6790.5
9	414.1267	6884	5.7	486	1473.5
10	631.1791	7984	6.6	801	650.8

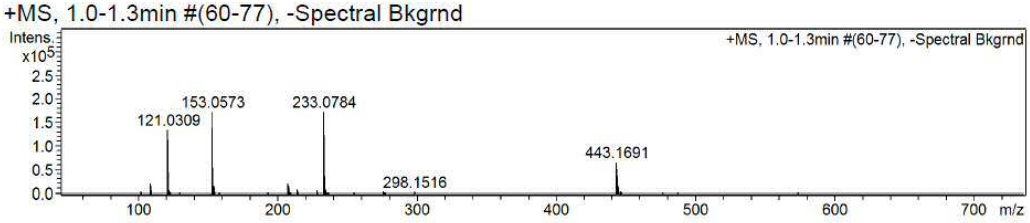
Methyl (3a*S*,7a*R*)-2,2-dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylate III-34



Confirmation of Expected Formula

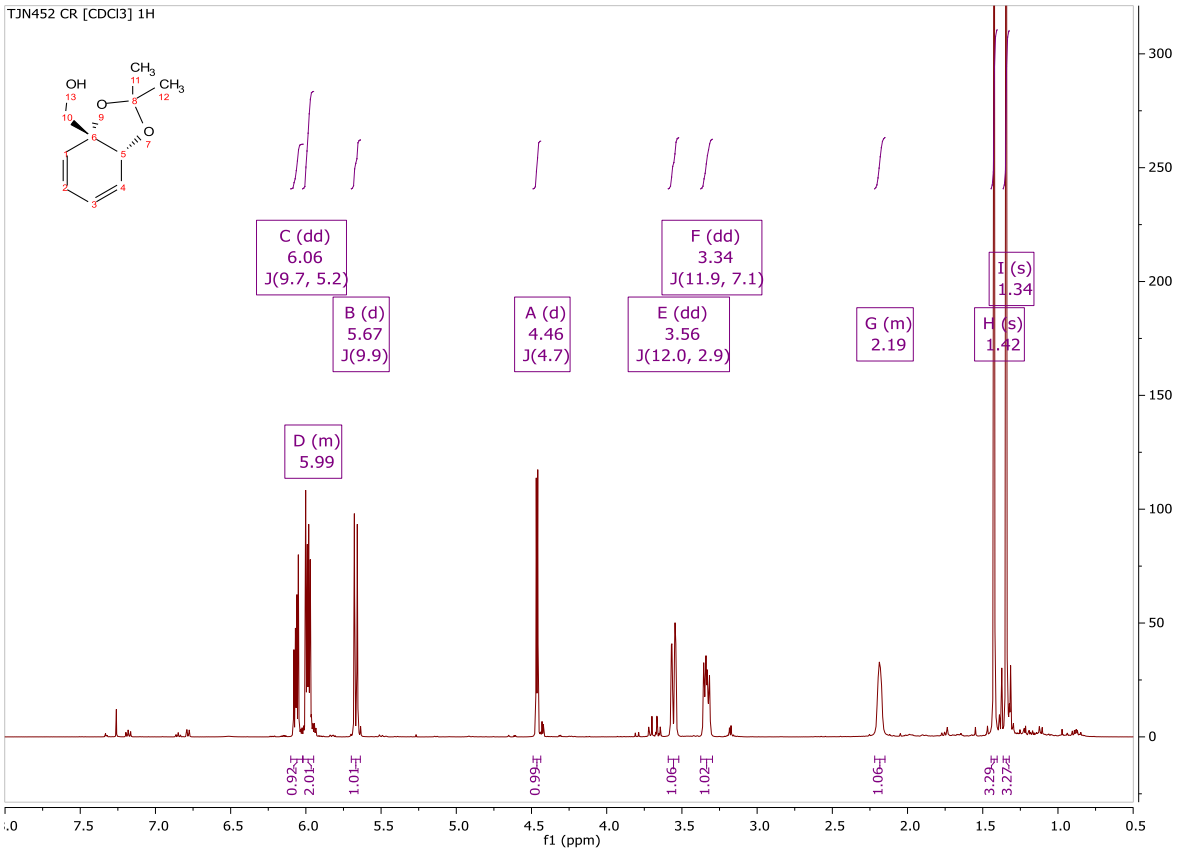
Sample-ID	tn_sel_tjn064	Submitter	Toby Nash
Analysis Name	tn_sel_tjn064_343890_30_01_48305.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	27/05/2015 12:30:28
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	109.0669	20282	11.7	449	2977.8
2	121.0309	134450	77.7	2811	15715.1
3	153.0573	172560	99.7	4524	13434.0
4	154.0601	15959	9.2	475	1229.6
5	207.0633	20967	12.1	909	1776.3
6	208.1839	16545	9.6	344	1348.1
7	233.0784	173017	100.0	6448	7623.3
8	234.0845	9381	5.4	408	405.8
9	443.1691	66514	38.4	5268	3282.1
10	444.1718	14064	8.1	1403	699.4

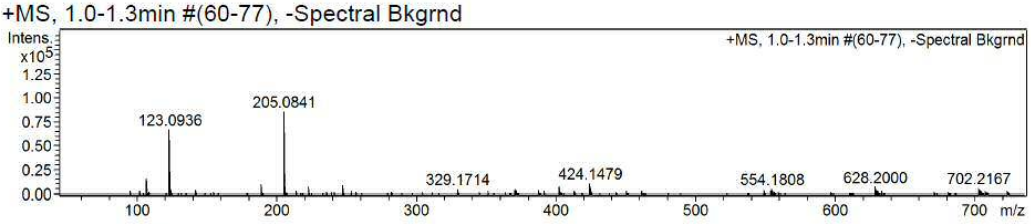
((3a*R*,7a*R*)-2,2-Dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methanol III-35



Confirmation of Expected Formula

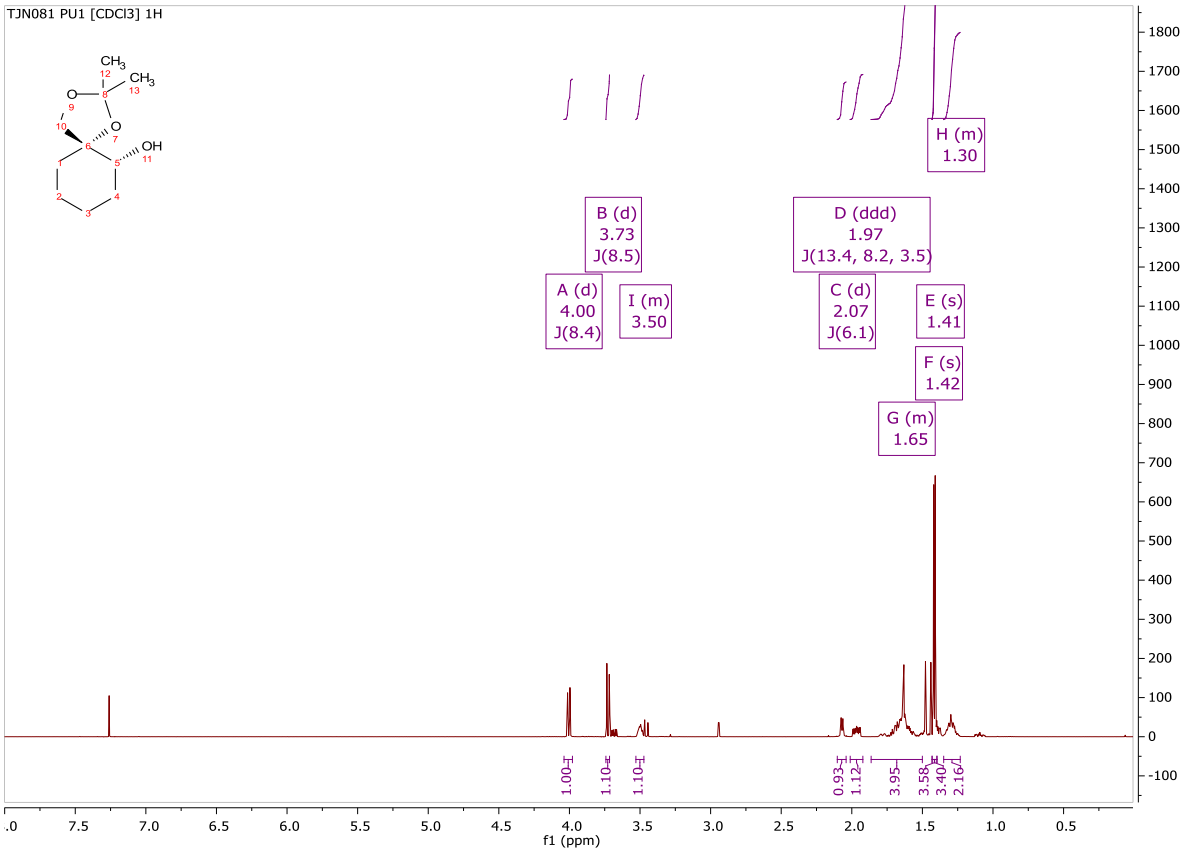
Sample-ID	tn_sel_065	Submitter	Toby Nash
Analysis Name	tn_sel_065_343960_17_01_48381.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	04/06/2015 14:57:32
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	107.0498	15699	18.4	257	2192.1
2	123.0936	67057	78.5	1572	8706.1
3	189.1096	10206	12.0	431	779.7
4	205.0841	85377	100.0	3405	4897.7
5	206.0873	9825	11.5	410	556.6
6	223.0926	8246	9.7	435	489.4
7	247.0933	9325	10.9	461	593.4
8	402.1694	8384	9.8	794	256.0
9	424.1479	11585	13.6	1012	315.1
10	628.2000	7624	8.9	1224	88.3

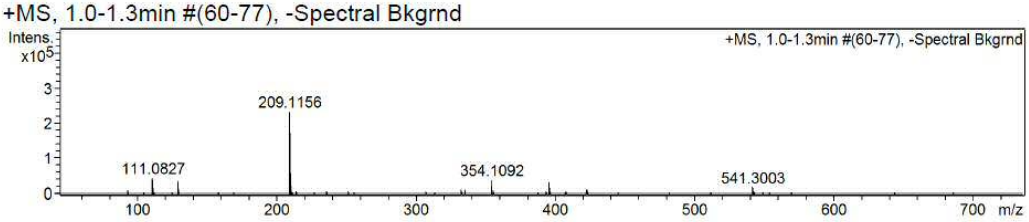
(5*R*,6*R*)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-ol III-30



Confirmation of Expected Formula

Sample-ID	tn_sel_TJN081	Submitter	Toby Nash
Analysis Name	tn_sel_TJN081 _344336_92_01_48788.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	17/07/2015 11:56:24
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



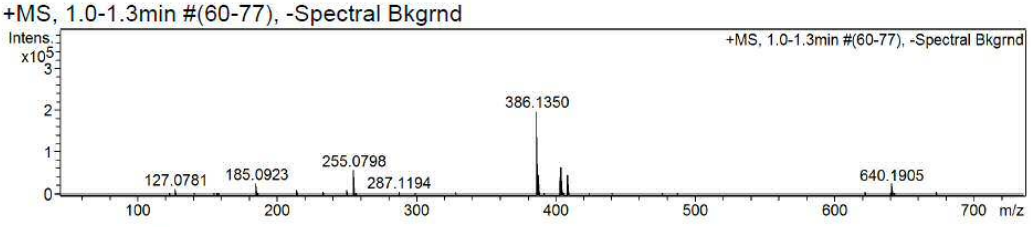
#	m/z	I	I %	Area	S/N
1	111.0827	44686	19.2	941	5576.7
2	129.0931	36676	15.7	953	4606.4
3	209.1156	233313	100.0	7983	6798.1
4	210.1183	27091	11.6	1193	797.7
5	332.1274	12140	5.2	889	341.4
6	335.1820	10876	4.7	704	295.8
7	354.1092	38852	16.7	2591	961.0
8	395.2400	34201	14.7	2632	836.6
9	422.1986	11610	5.0	968	292.7
10	541.3003	17771	7.6	2340	371.3

Methyl (3a*S*,4*R*,10*S*,10a*R*)-2,2-dimethyl-6,8-dioxo-7-phenyl-7,8,10,10a-tetrahydro-6H-4,10-etheno[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a(4H)-carboxylate III-42

Confirmation of Expected Formula

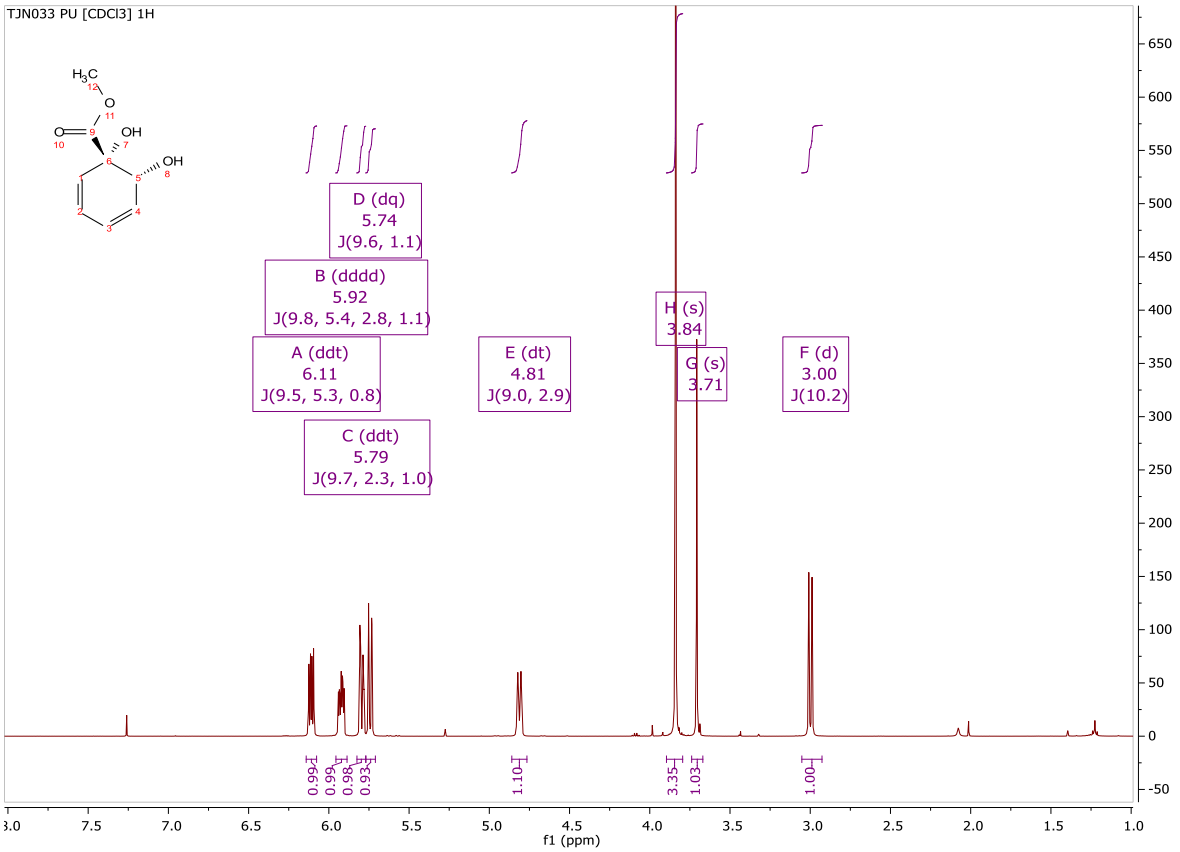
Sample-ID	tn_sel_TJN088	Submitter	Toby Nash
Analysis Name	tn_sel_TJN088_344757_14_01_49279.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	25/08/2015 09:21:50
Ionisation Mode	positive electrospray (ESI)		

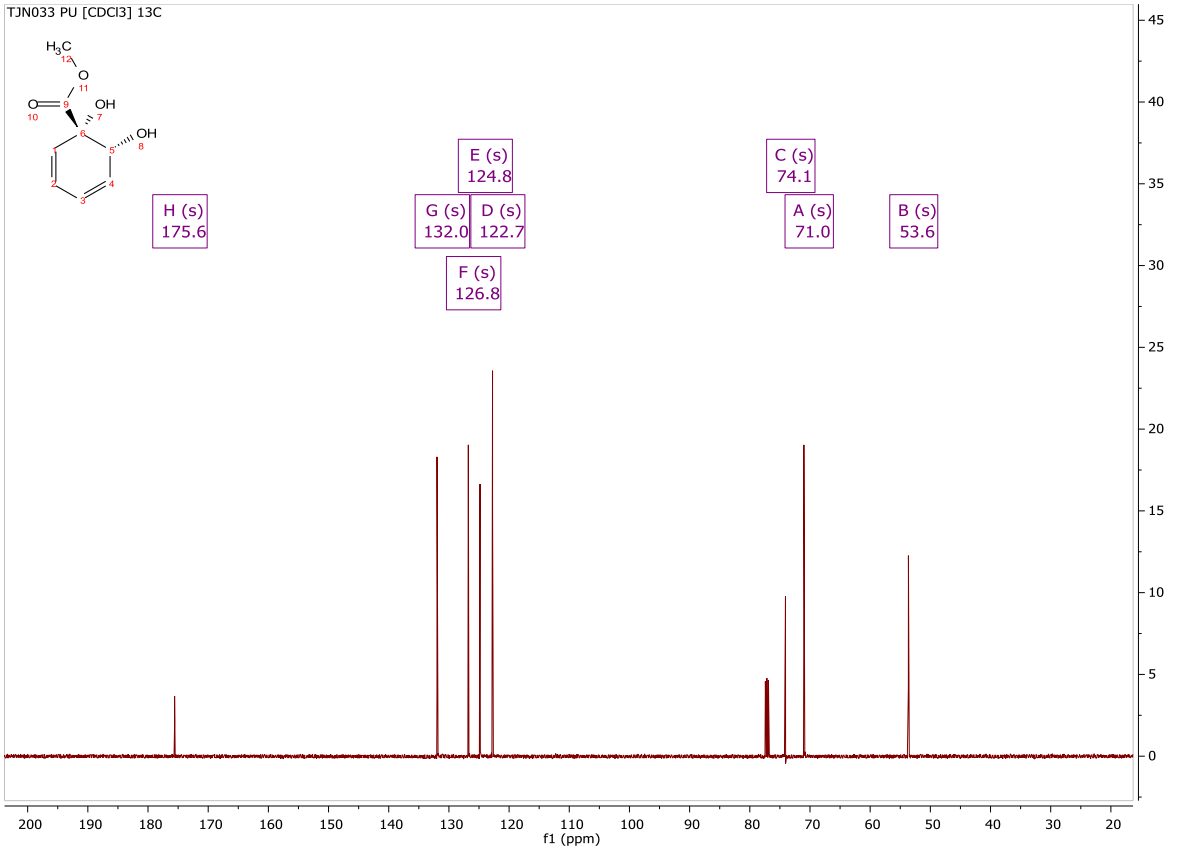
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



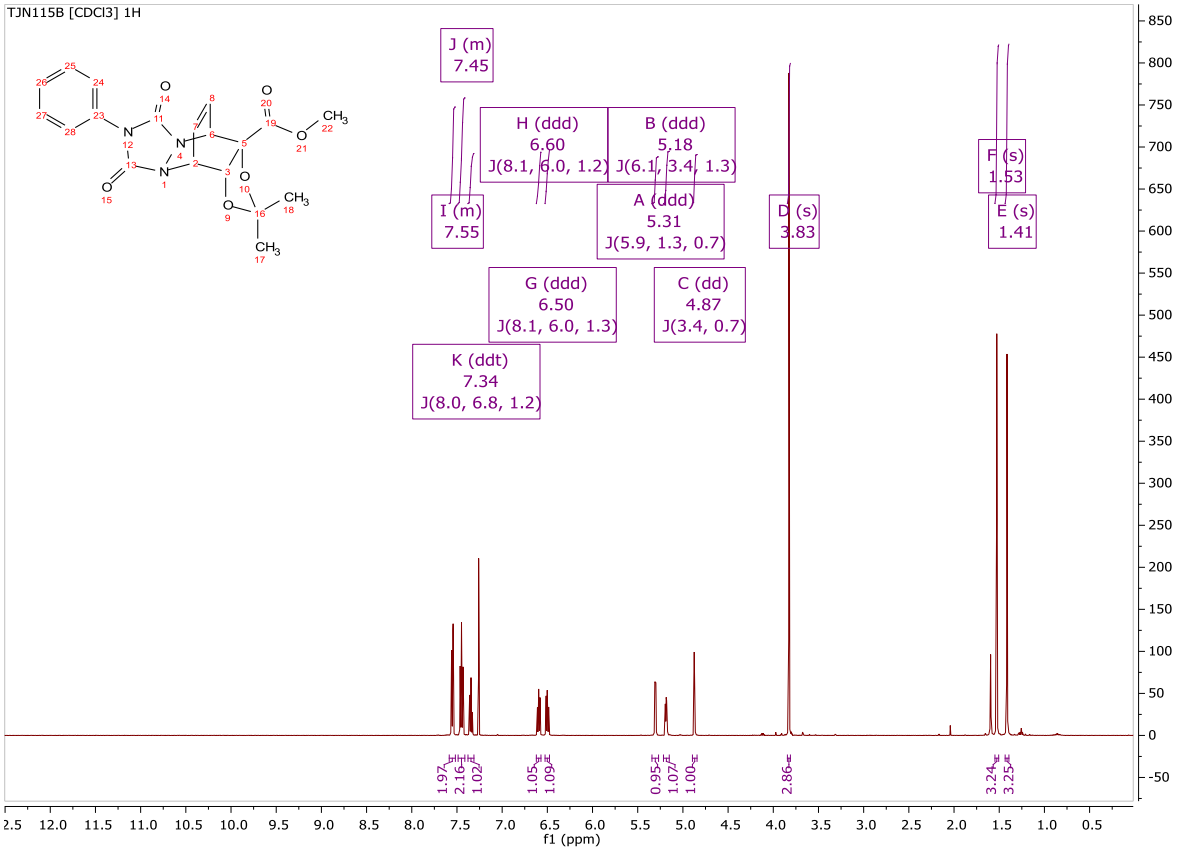
#	m/z	I	I %	Area	S/N
1	127.0781	11619	5.9	215	6335.3
2	185.0923	24929	12.7	445	4973.1
3	214.1061	8950	4.6	222	1042.4
4	255.0798	56574	28.9	1109	3767.9
5	386.1350	195814	100.0	12261	4872.9
6	387.1347	45500	23.2	3509	1107.2
7	403.1585	63084	32.2	4852	1943.3
8	404.1627	12576	6.4	1115	397.9
9	408.1149	46330	23.7	4047	1641.5
10	640.1905	22745	11.6	3614	1451.6

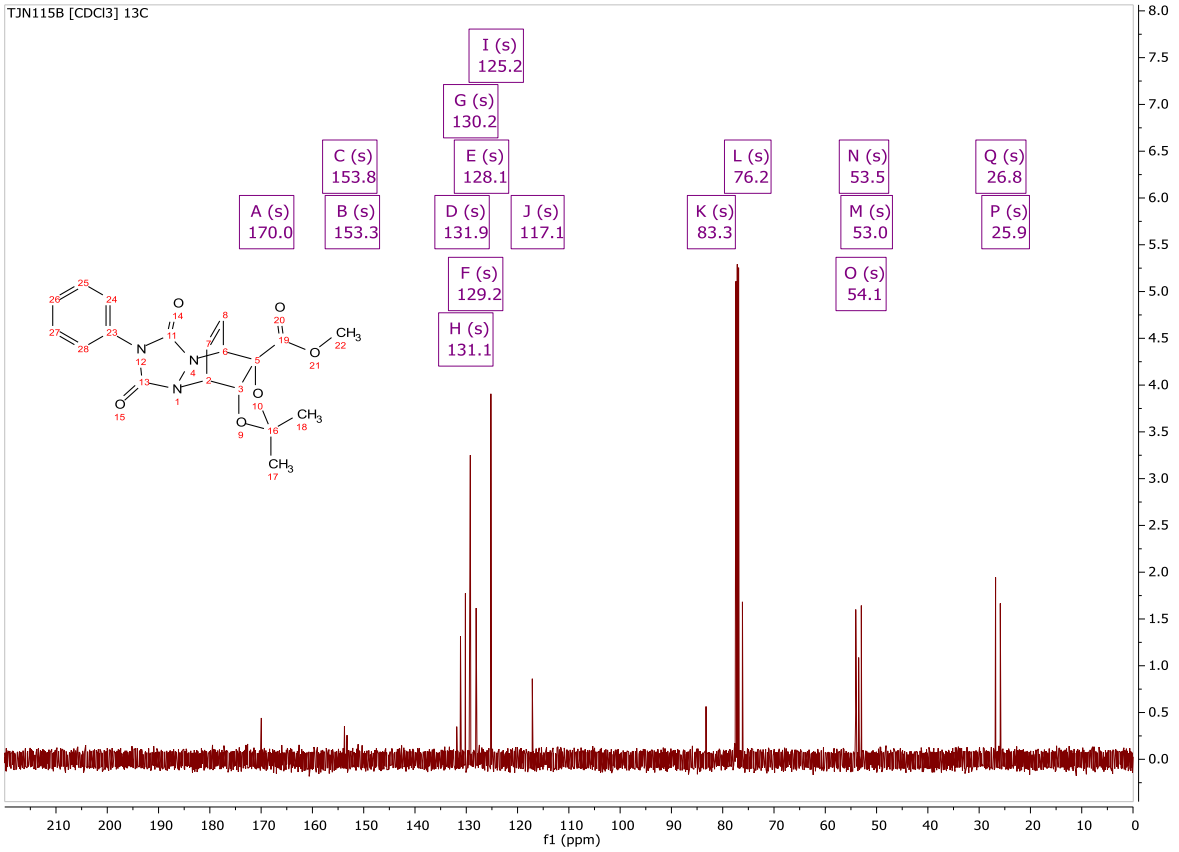
Methyl (1*S*,6*R*)-1,6-dihydroxycyclohexa-2,4-diene-1-carboxylate III-43



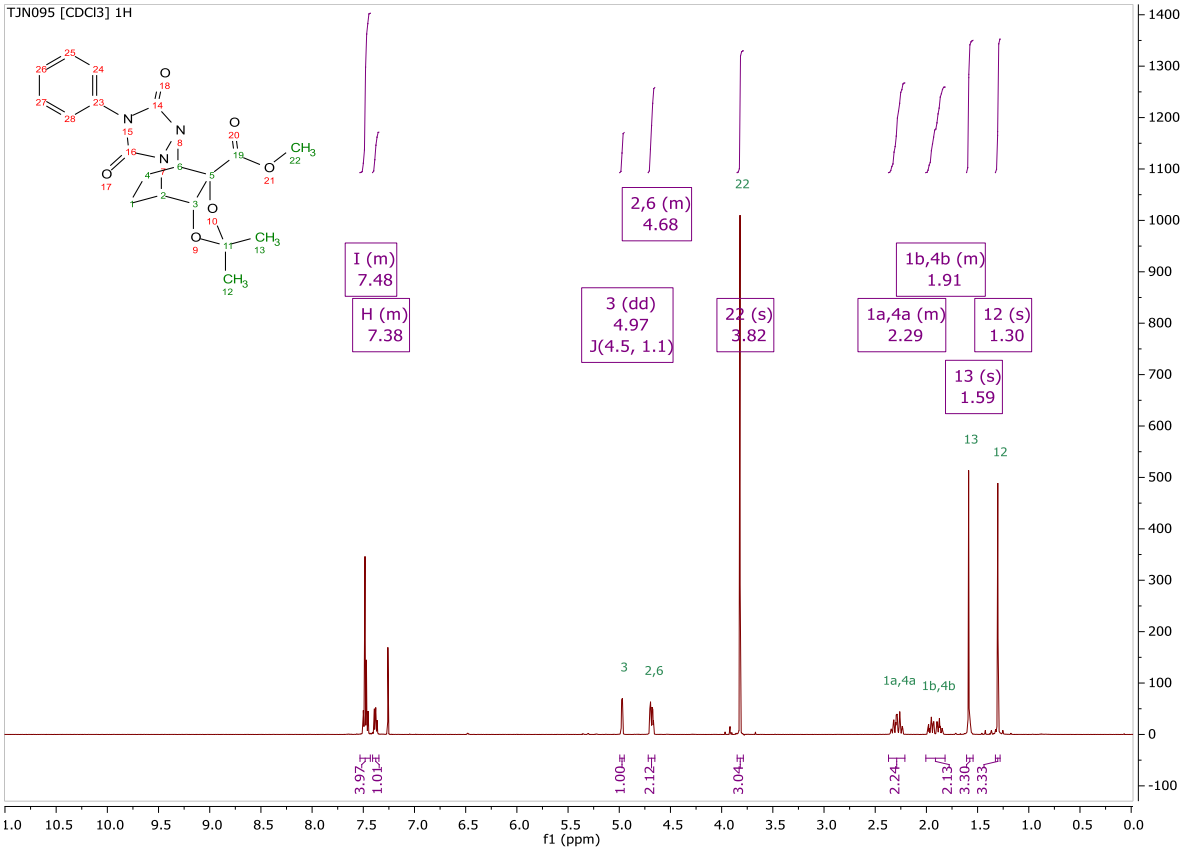


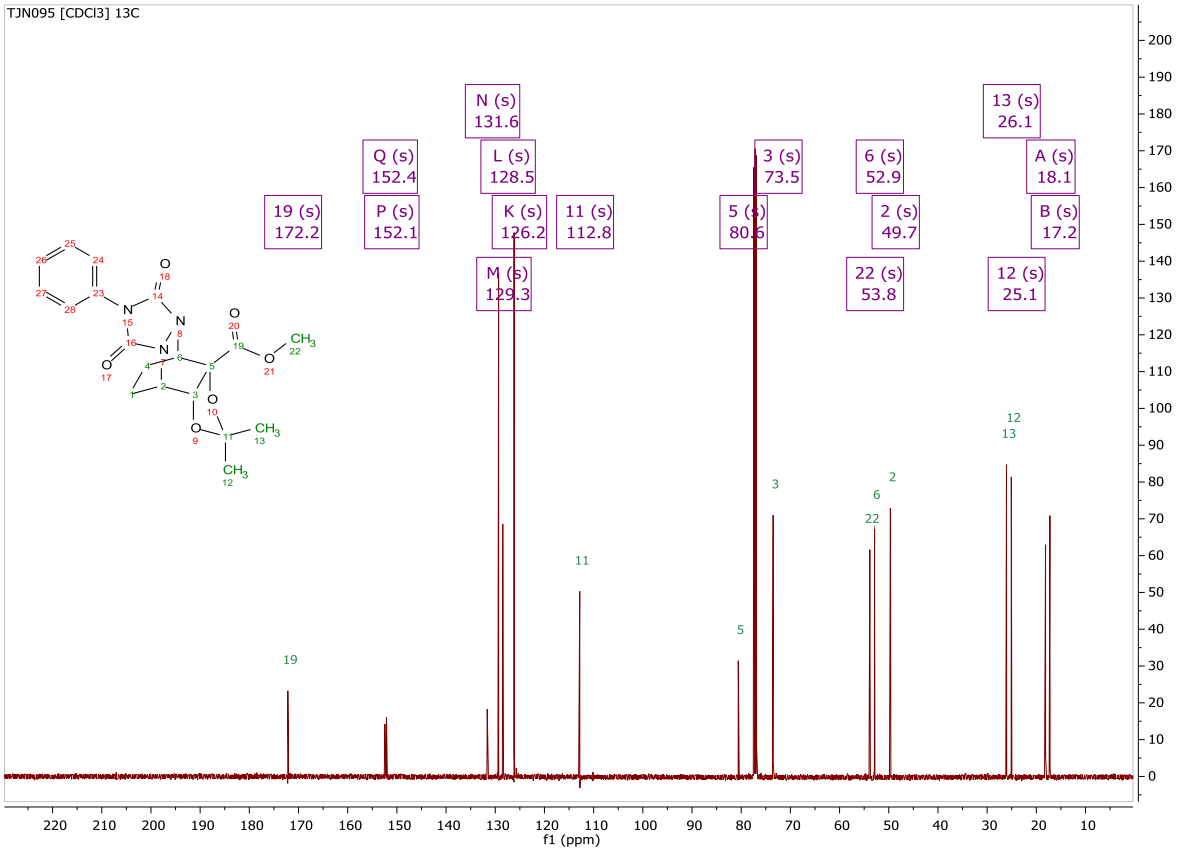
Methyl (3a*S*,4*S*,10*R*,10a*R*)-2,2-dimethyl-6,8-dioxo-7-phenyl-7,8,10,10a-tetrahydro-6H-4,10-etheno[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a(4H)-carboxylate III-46

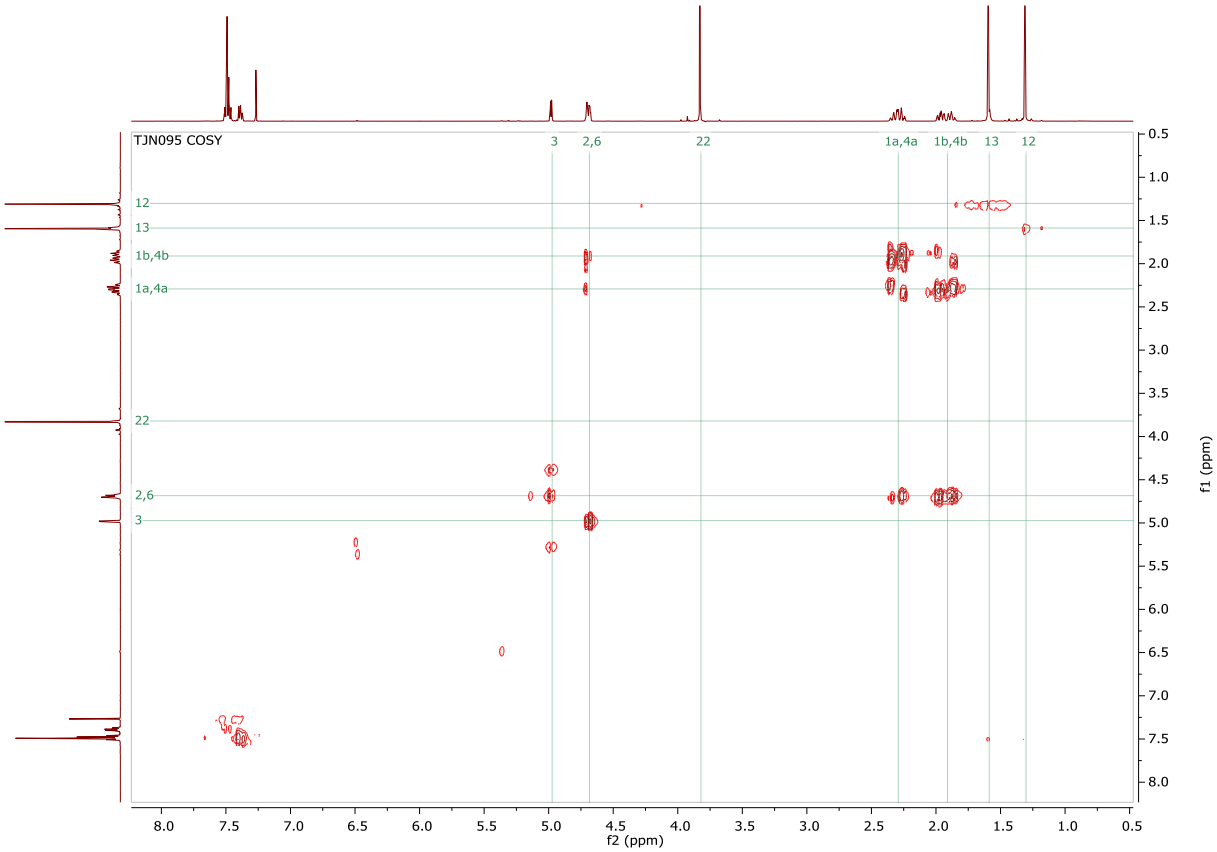


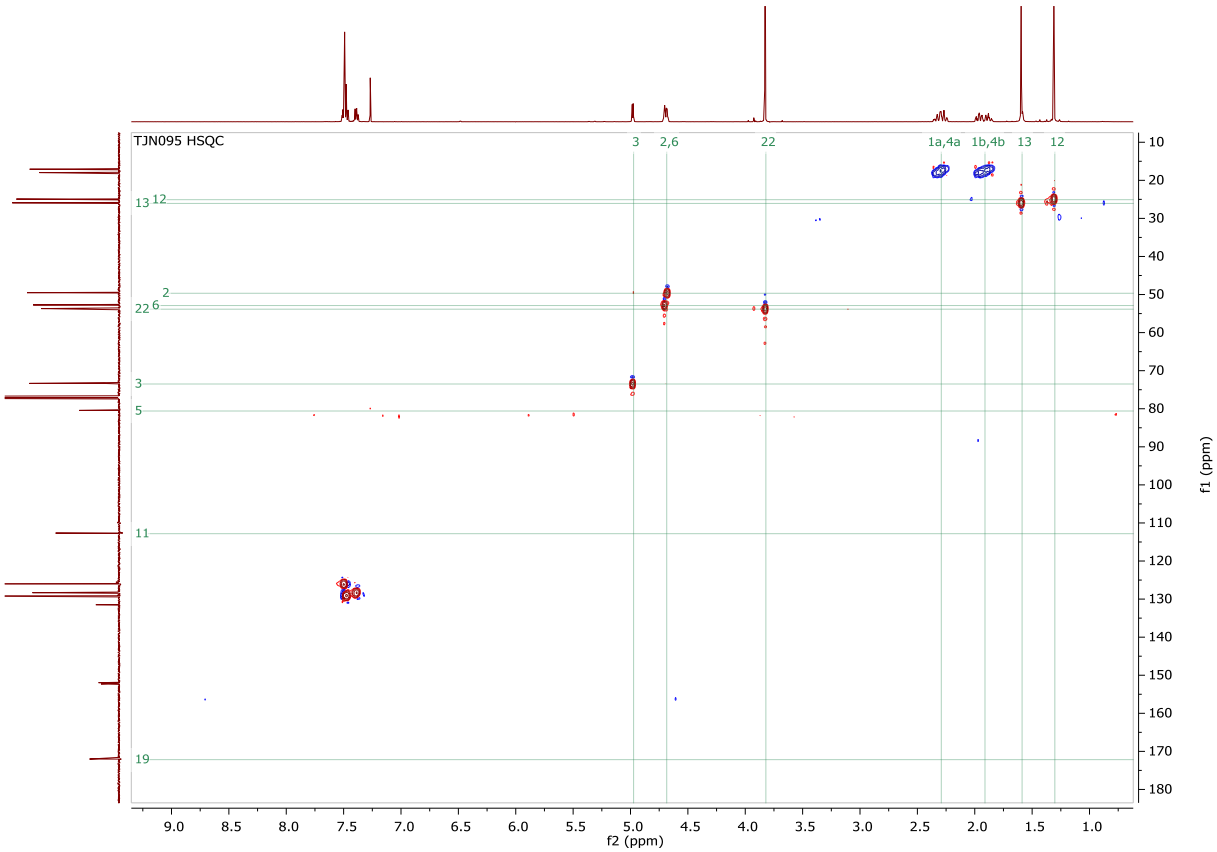


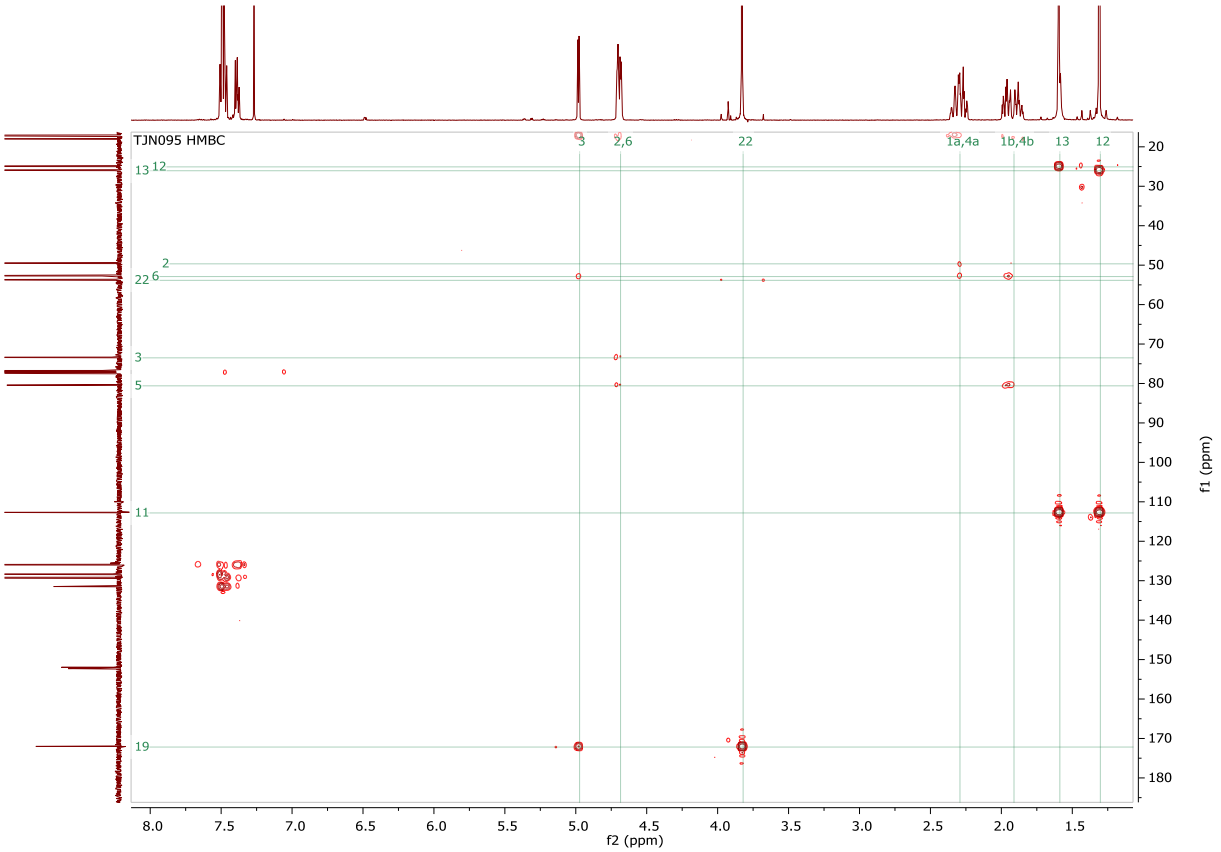
Methyl (3a*S*,4*R*,10*S*,10a*R*)-2,2-dimethyl-6,8-dioxo-7-phenyltetrahydro-6H-4,10-ethano[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a(4H)-carboxylate III-47






TJN095 COSY
3
2,6
22
1a,4a
1b,4b
13
12
12
13
1b,4b
1a,4a
22
2,6
3
f2 (ppm)
f1 (ppm)

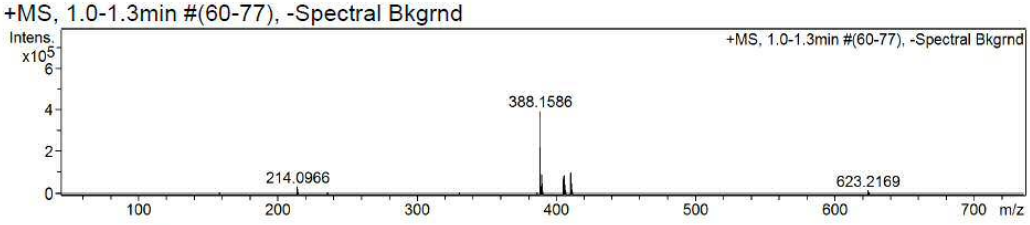

TJN095 HSQC
3
2,6
22
1a,4a
1b,4b
13
12
13
12
2
22
6
3
5
11
19
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

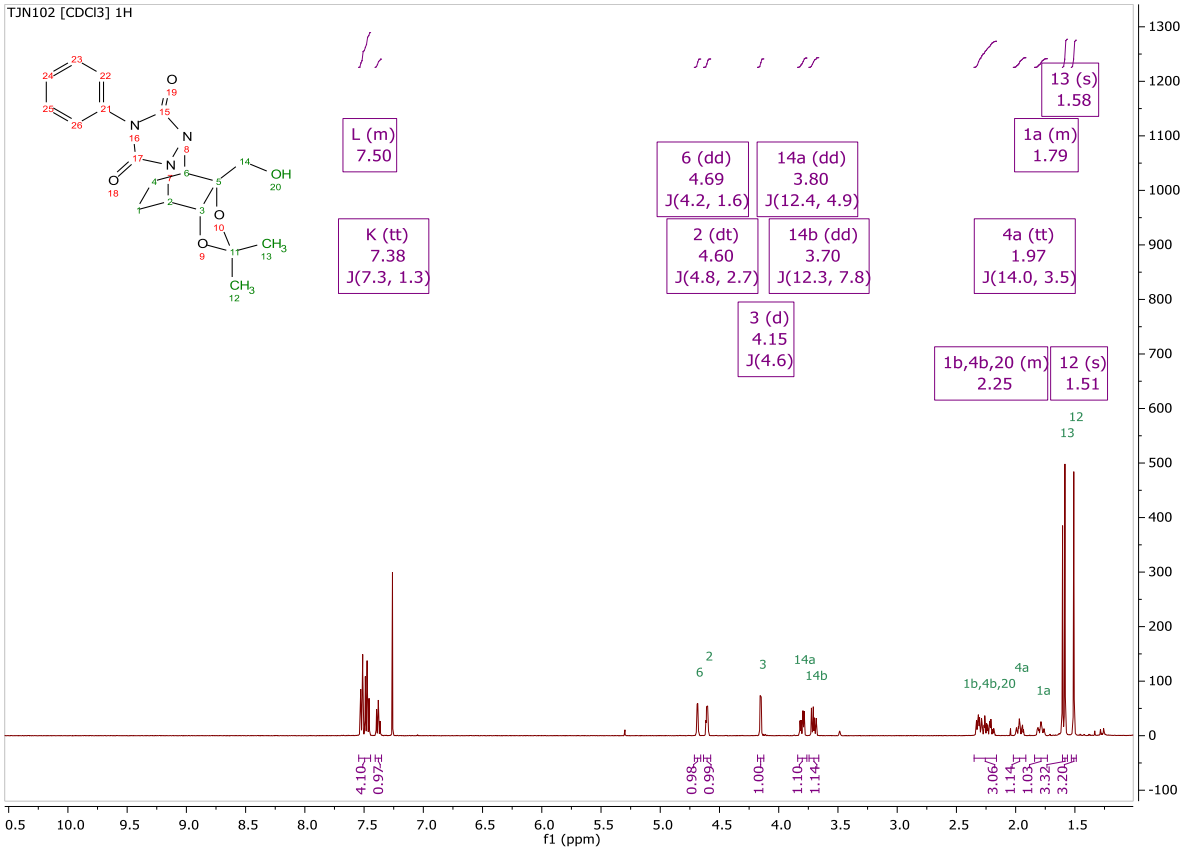
Sample-ID	tn_sel_TJN095	Submitter	Toby Nash
Analysis Name	tn_sel_TJN095_344865_39_01_49388.d	Supervisor	Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	09/09/2015 10:21:40
Ionisation Mode	positive electrospray (ESI)		

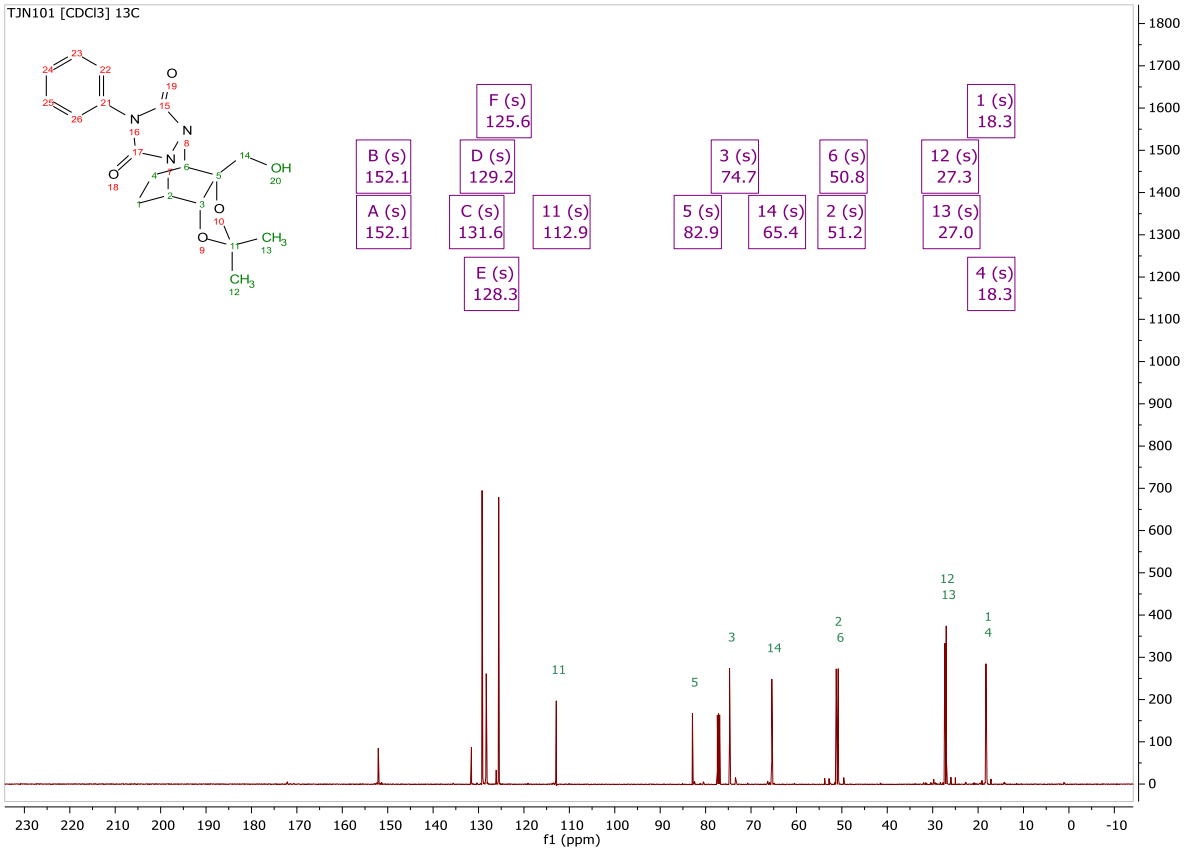
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

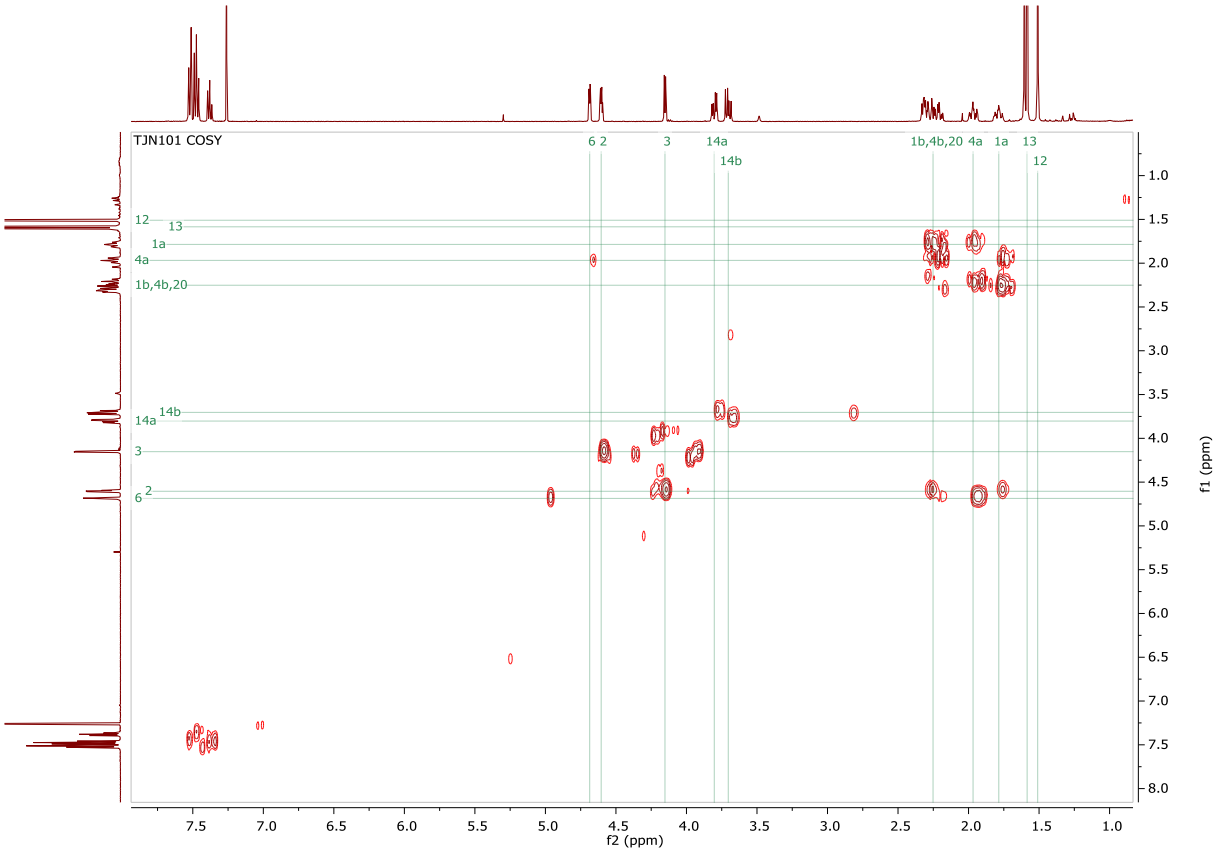


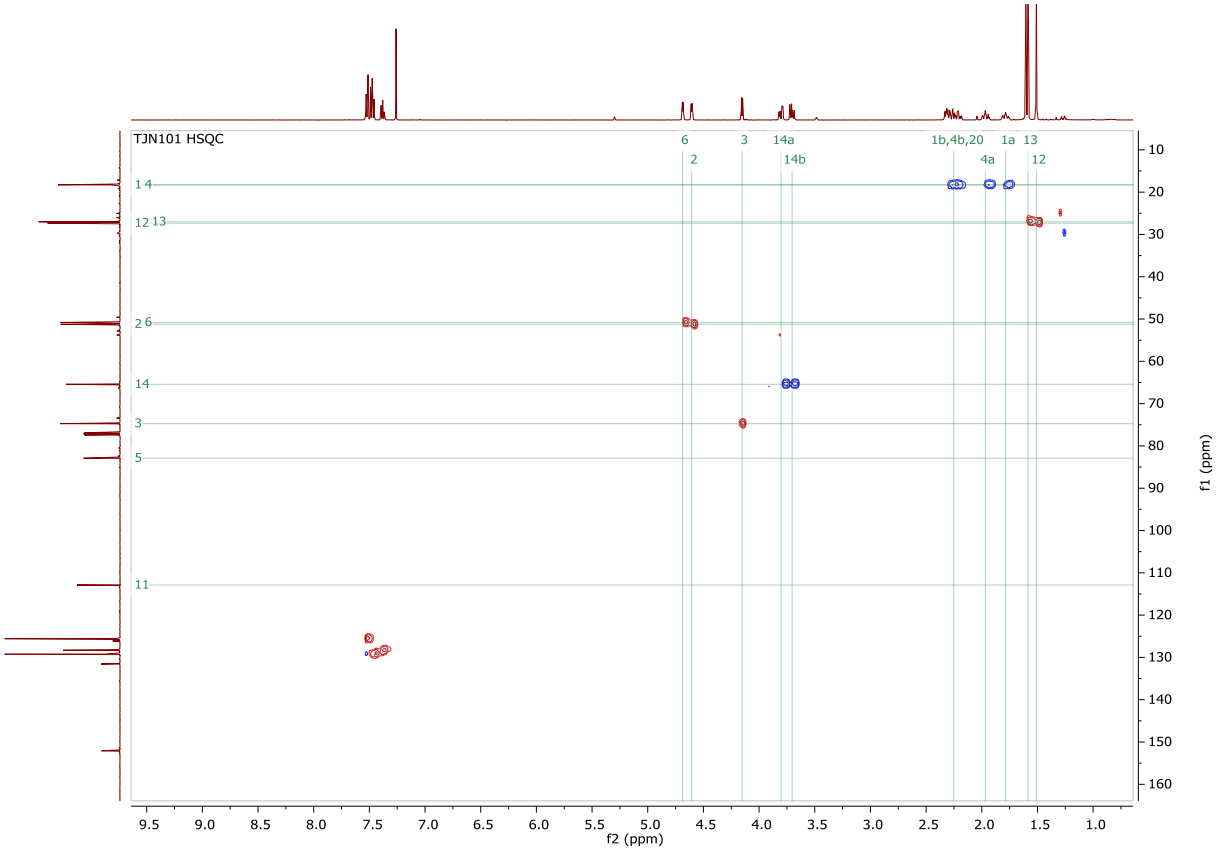
#	m/z	I	I %	Area	S/N
1	158.0345	7756	2.0	116	4579.5
2	214.0966	32585	8.3	532	8757.2
3	388.1586	392164	100.0	17711	4181.7
4	389.1542	90358	23.0	6397	943.1
5	390.1589	14625	3.7	1117	150.3
6	405.1799	89589	22.8	6804	1305.3
7	406.1826	19876	5.1	1659	297.9
8	410.1344	100000	25.5	7244	1689.7
9	411.1404	20052	5.1	1565	350.2
10	623.2169	13119	3.3	1802	661.8

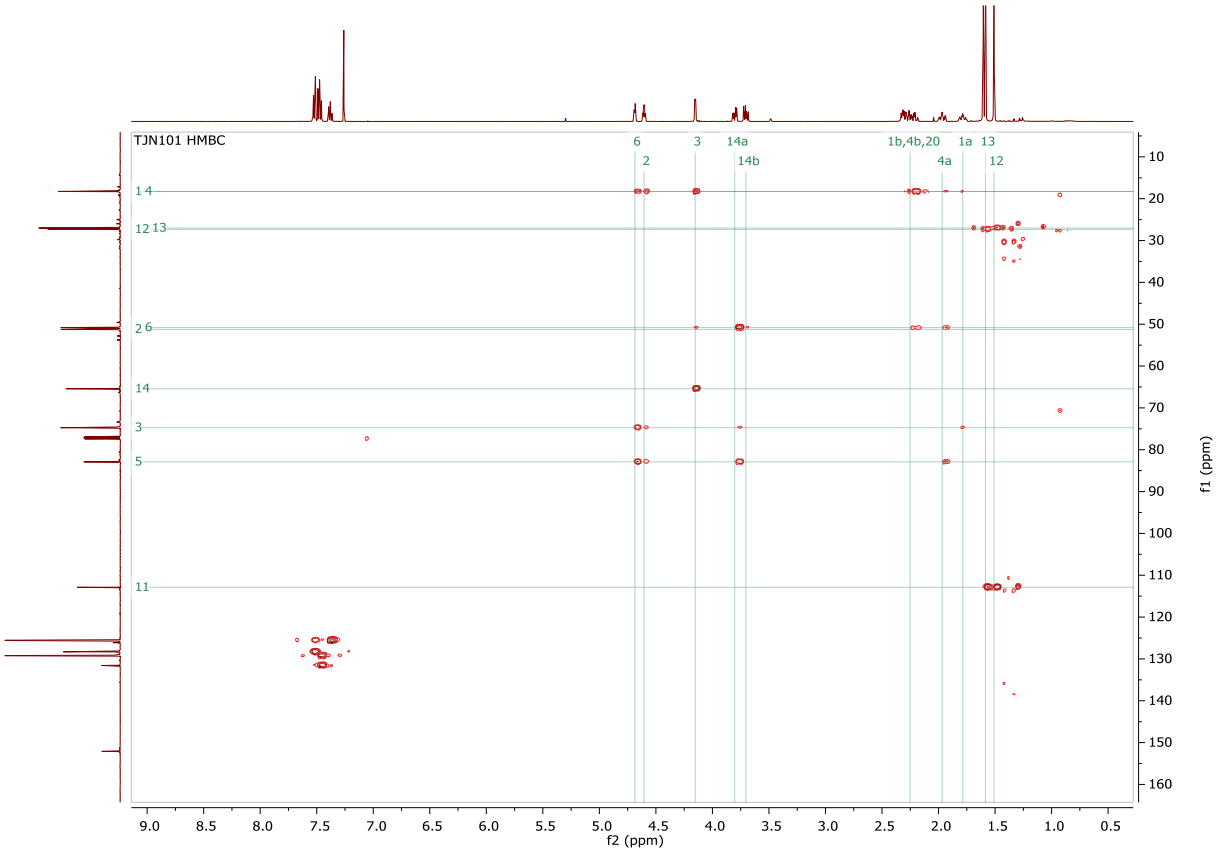
(3a*R*,4*R*,10*S*,10a*R*)-3a-(Hydroxymethyl)-2,2-dimethyl-7-phenyltetrahydro-6H-4,10-ethano[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-6,8(7H)-dione III-48






TJN101 COSY
6 2
3
14a
14b
1b,4b,20
4a
1a
13
12
f2 (ppm)
f1 (ppm)


TJN101 HSQC
6
2
3
14a
14b
1b,4b,20
4a
1a
13
12
11
5
f2 (ppm)
f1 (ppm)

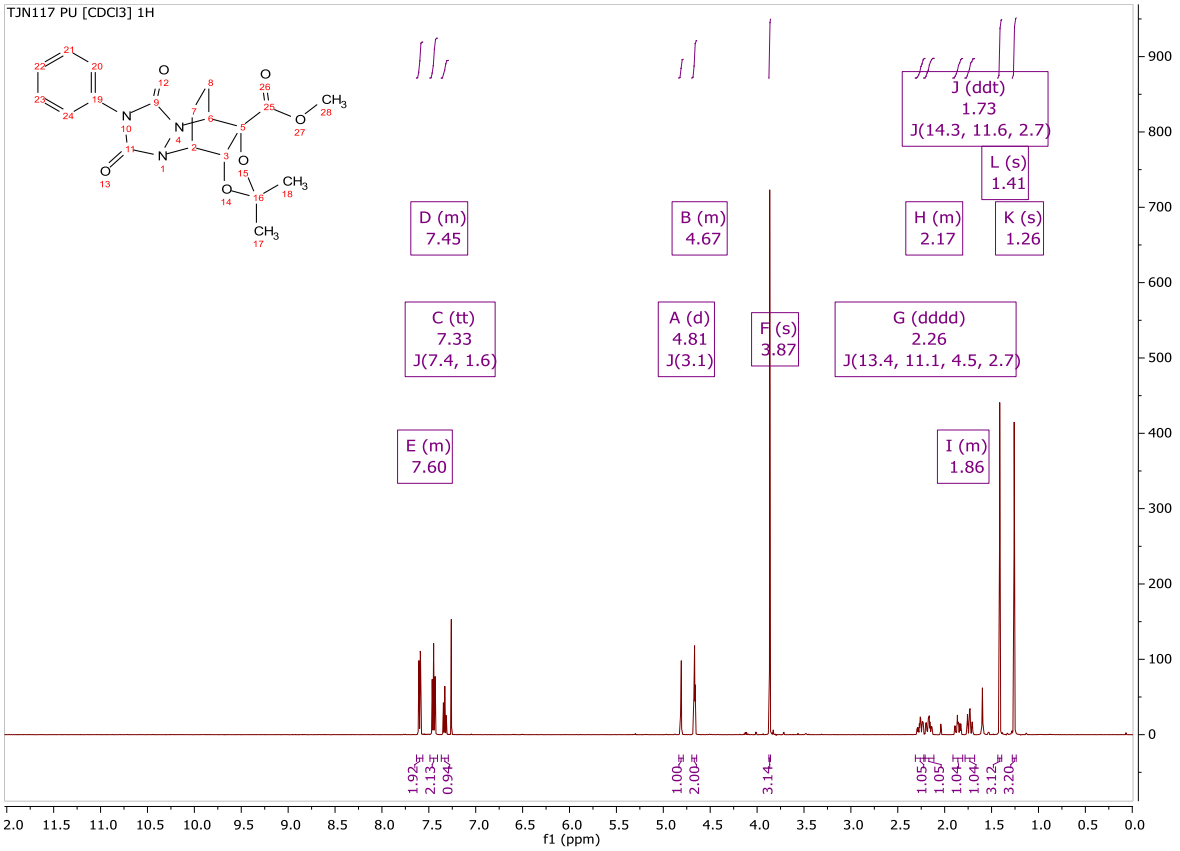


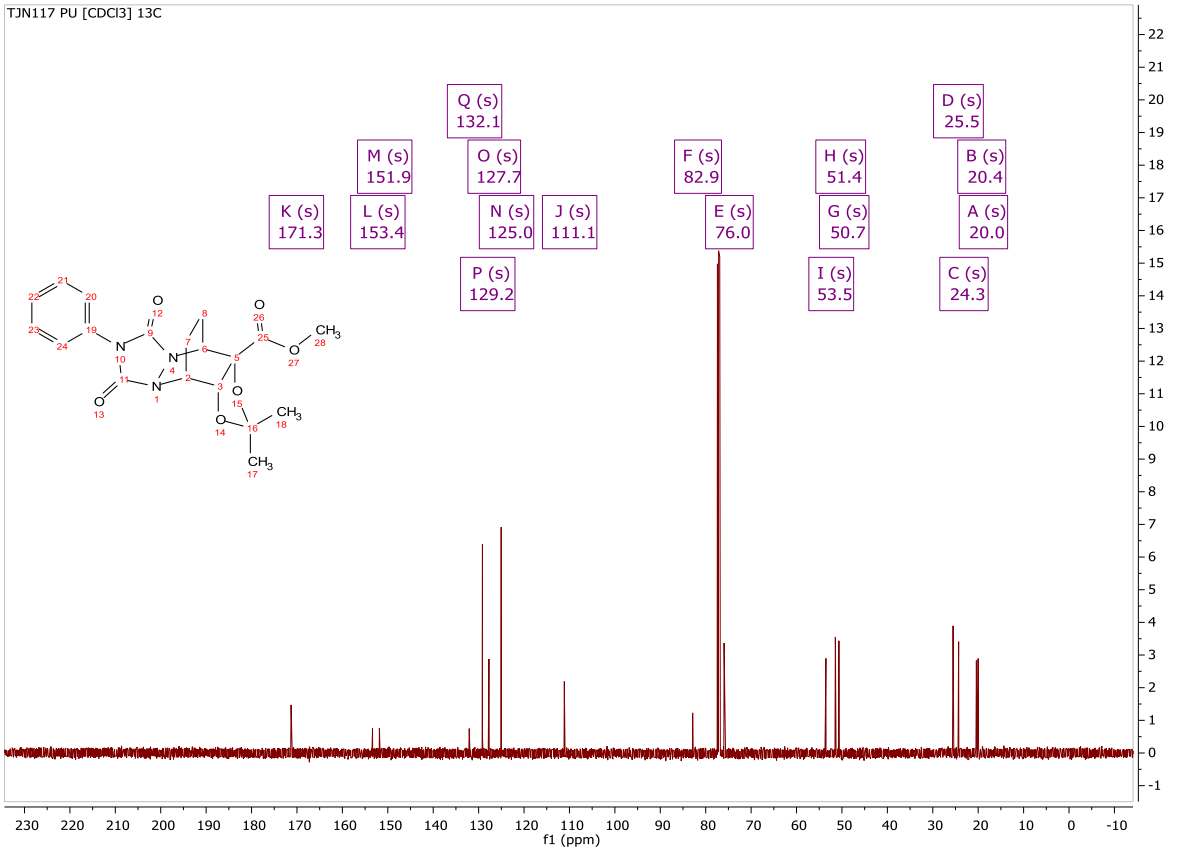
Bruker Daltonics Compass OpenAccess 1.3.0 - Results of job 77342 - Fri Sep 14 14:33:45 BST 2018

Results of job 77342

Sample	Sample Description	Method	Submitter	Pos	Expected Formula	Project	Peaknumber	meas. m/z	theo. m/z	err[ppm]	sigma	Formulae
tn_sel_TJNT02		Confirm Formula Positive 50to500 loop inj	tjn30 Toby Nash		C18 H21 N3 O5	TJN102	1	360.155600	360.1554	0.5	0.0043	C 18 H 22 N 3 O 5

Methyl (3a*S*,4*S*,10*R*,10a*R*)-2,2-dimethyl-6,8-dioxo-7-phenyltetrahydro-6H-4,10-ethano[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-3a(4H)-carboxylate III-49



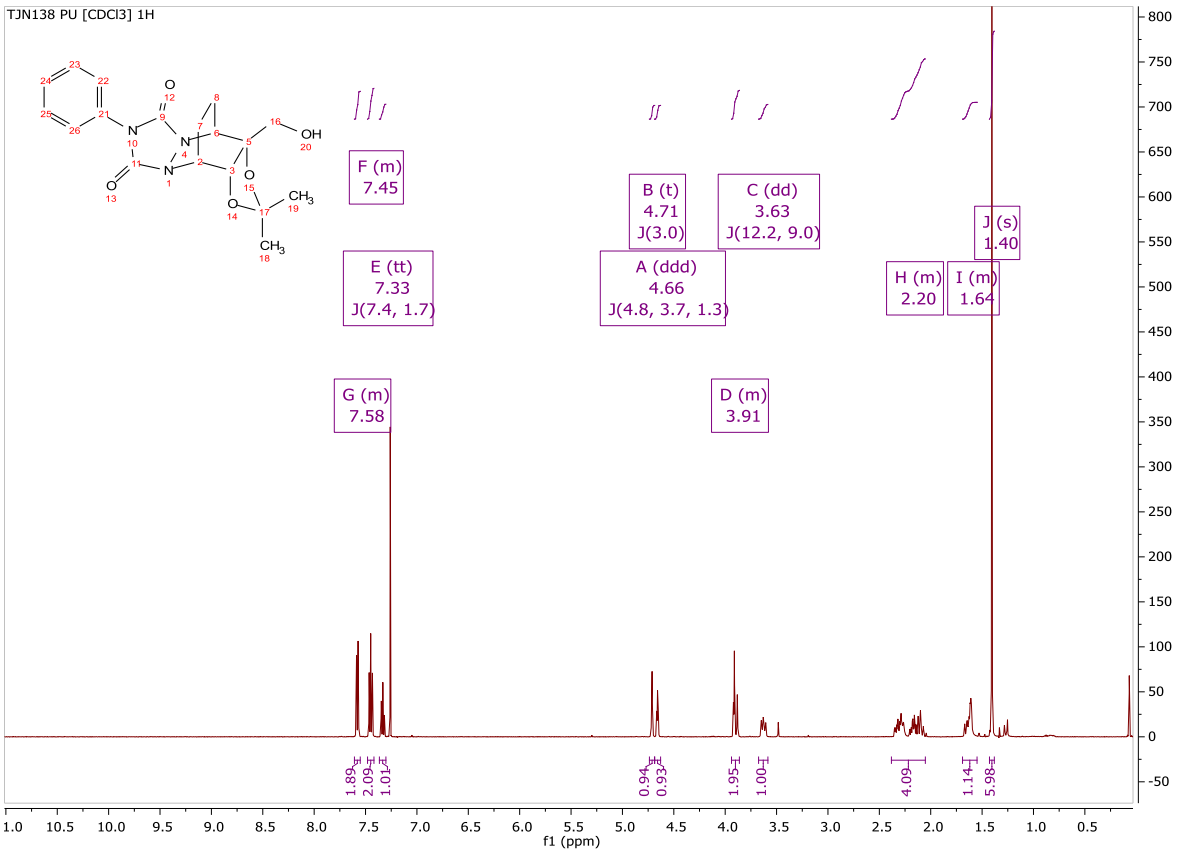


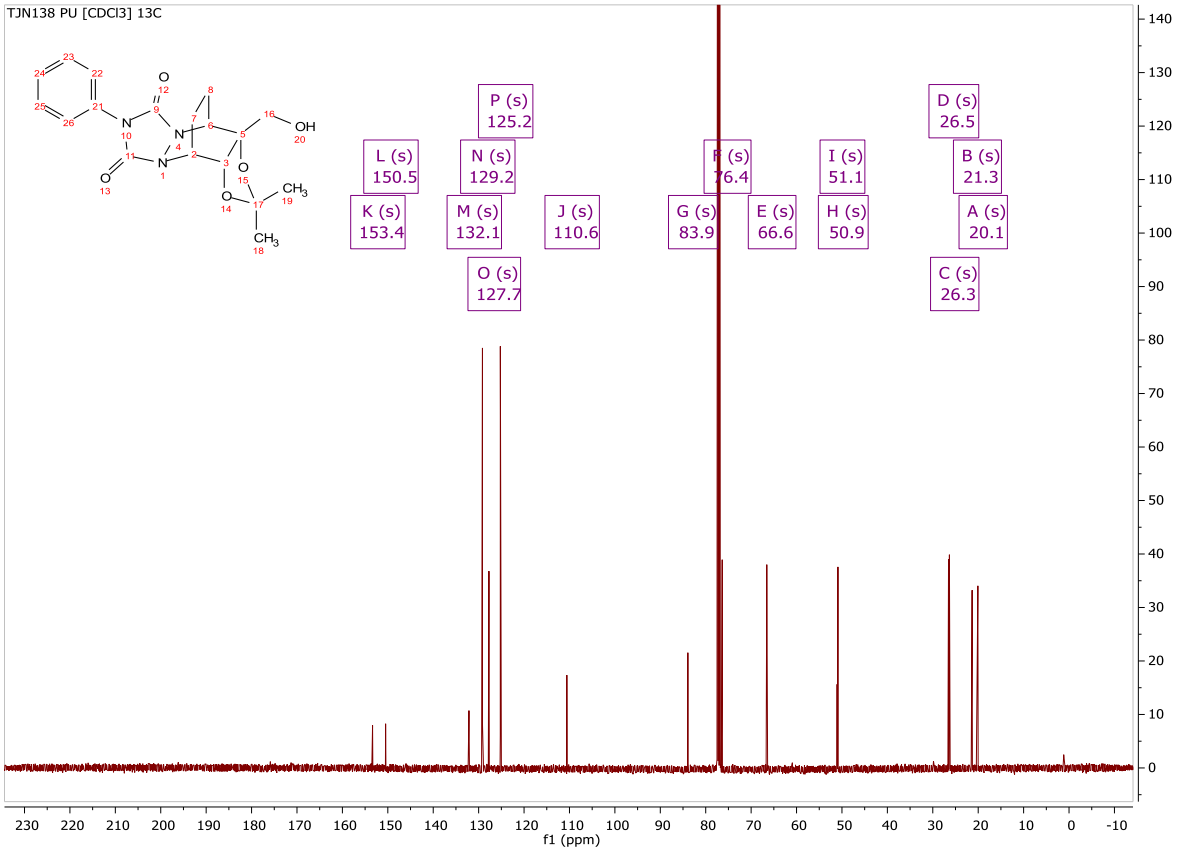
Bruker Daltonics Compass OpenAccess 1.3.0 - Results of job 77343 - Fri Sep 14 14:35:00 BST 2018

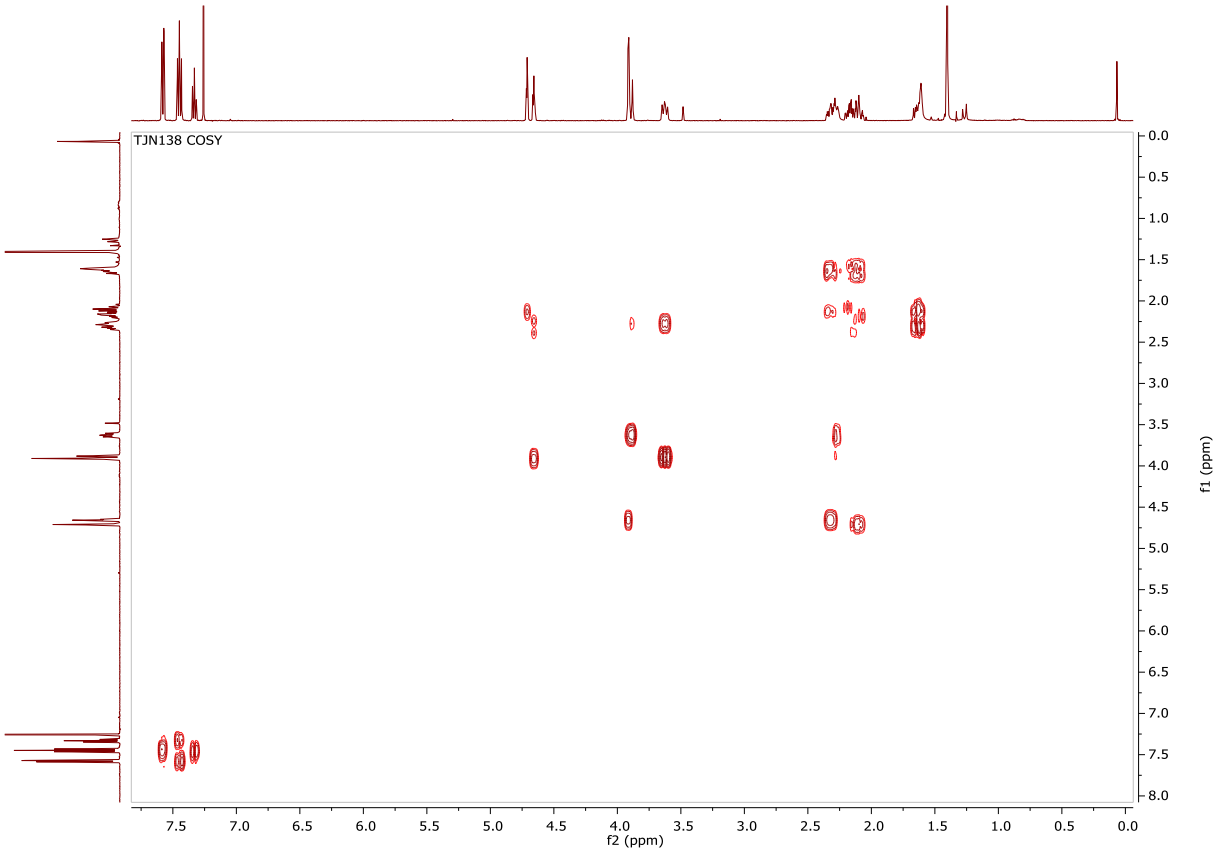
Results of job 77343

Sample	Sample Description	Method	Submitter	Pos	Expected Formula	Project	Peaknumber	meas. m/z	theo. m/z	err[ppm]	sigma	Formulae
tn_sel_TJN117		Confirm Formula Positive 50to500 loop inj	tjn30 Toby Nash		C19 H21 N3 O6	TJN117	1	388.151900	388.1503	4	0.0018	C 19 H 22 N 3 O 6

(3a*R*,4*S*,10*R*,10a*R*)-3a-(Hydroxymethyl)-2,2-dimethyl-7-phenyltetrahydro-6H-4,10-ethano[1,3]dioxolo[4,5-d][1,2,4]triazolo[1,2-a]pyridazine-6,8(7H)-dione III-50





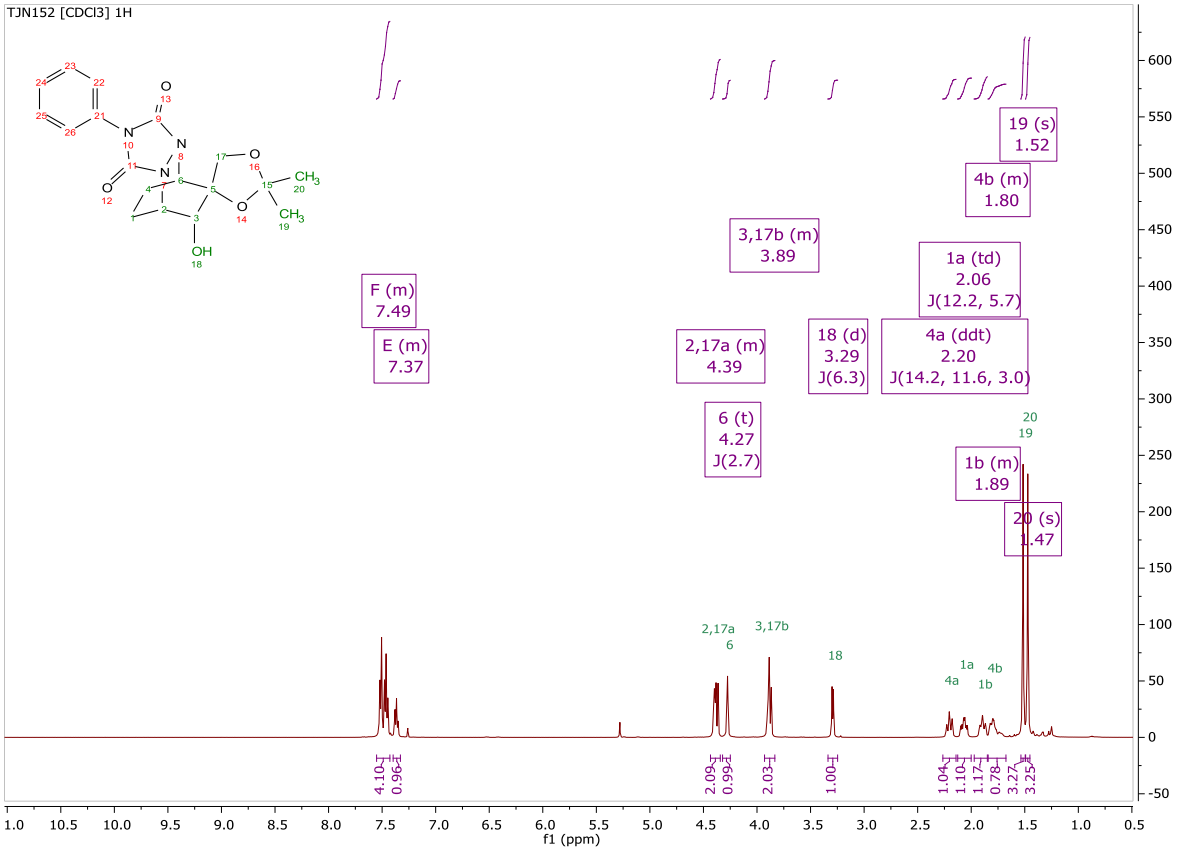


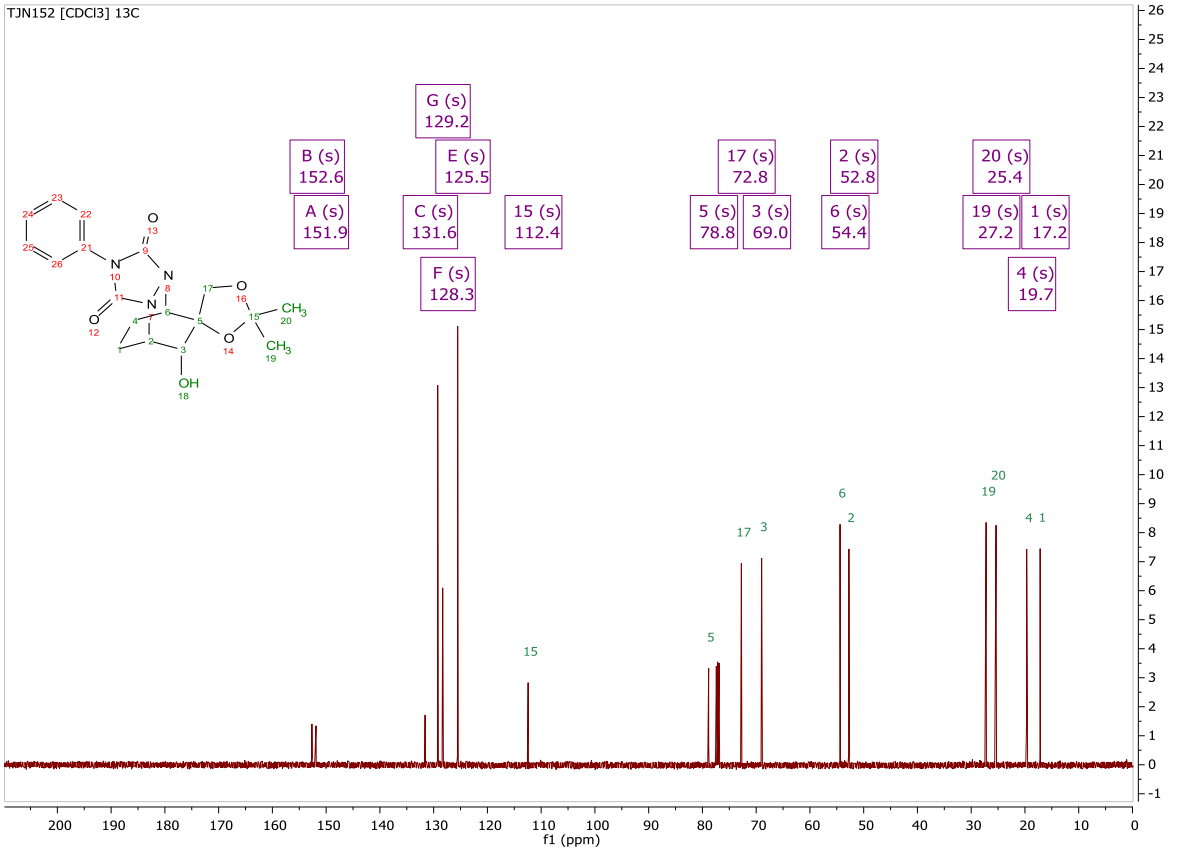
Bruker Daltonics Compass OpenAccess 1.3.0 - Results of job 77344 - Fri Sep 14 14:35:17 BST 2018

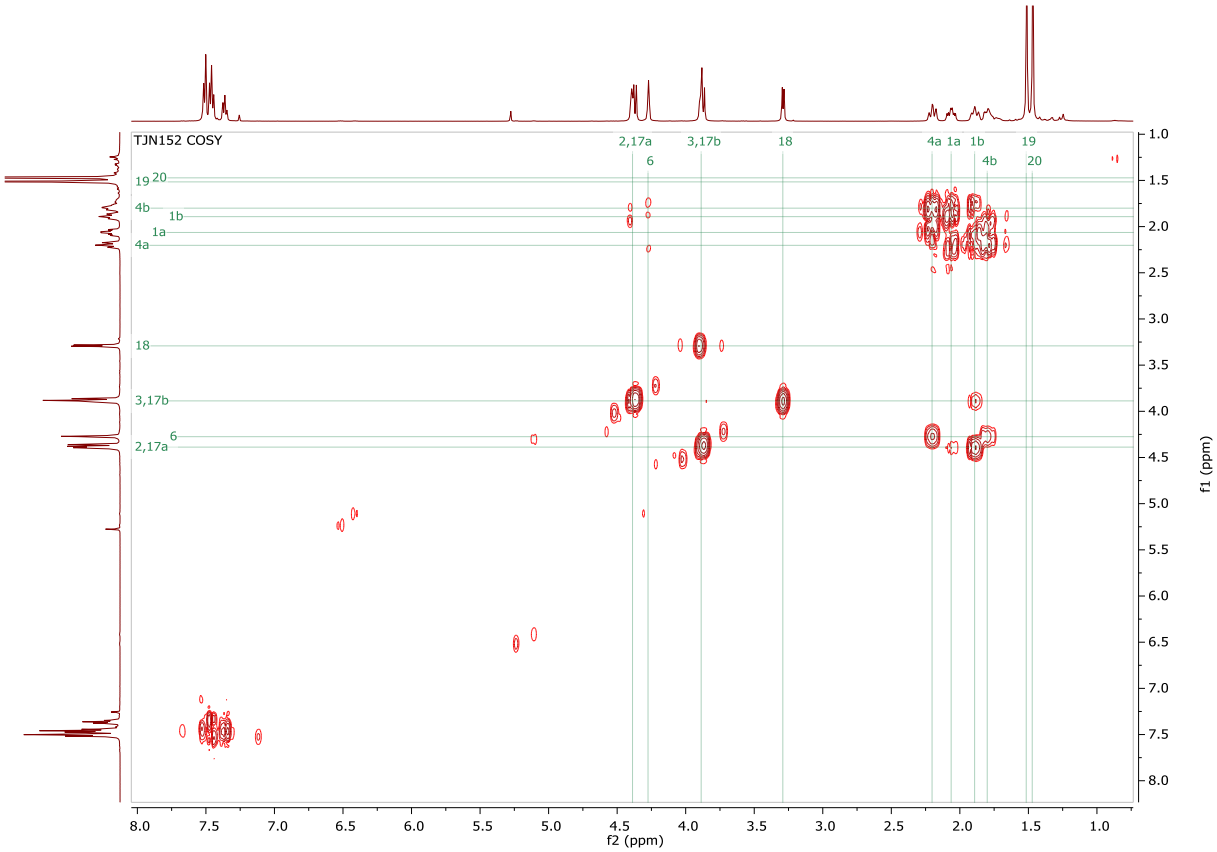
Results of job 77344

Sample	Sample Description	Method	Submitter	Pos	Expected Formula	Project	Peaknumber	meas. m/z	theo. m/z	err[ppm]	sigma	Formulae
tn_sel_TJN138		Confirm Formula Positive 50to500 loop inj	tjn30 Toby Nash		C18 H21 N3 O5	TJN138	1	360.155100	360.1554	-0.8	0.0163	C 18 H 22 N 3 O 5

(4*R*,5'*R*,7'*R*,8'*S*)-7'-Hydroxy-2,2-dimethyl-2'-phenyldihydro-1'H,5'H-spiro[[1,3]dioxolane-4,6'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3'(2'H)-dione III-52






TJN152 COSY
2,17a
6
3,17b
18
4a
1a
1b
4b
19
20
f2 (ppm)
f1 (ppm)


TJN152 HSQC
2,17a
6
3,17b
18
4a
1a
1b
4b
19
20
15
f2 (ppm)
f1 (ppm)

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Results of job 77346

Sample	Sample Description	Method	Submitter	Pos	Expected Formula	Project	Peaknumber	meas. m/z	theo. m/z	err[ppm]	sigma	Formulae
tn_sel_TJN152		Confirm Formula Positive 50to500 loop inj	tjn30 Toby Nash		C18 H21 N3 O5	TJN152	1	360.156000	360.1554	1.7	0.0025	C 18 H 22 N 3 O 5

Crystal structure data for III-52

Table 1. Crystal data and structure refinement for s16sel2.

Identification code	s16sel2	
Empirical formula	C18 H21 N3 O5	
Formula weight	359.38	
Temperature	150.00(10) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.69840(10) Å	α= 90°.
	b = 11.9848(2) Å	β= 90°.
	c = 21.2306(3) Å	γ = 90°.
Volume	1704.37(5) $Å^3$	
Z	4	
Density (calculated)	1.401 Mg/m^3	
Absorption coefficient	0.862 mm^{-1}	
F(000)	760	
Crystal size	0.300 x 0.200 x 0.080 mm^3	
Theta range for data collection	4.165 to 73.004°.	
Index ranges	-8<=h<=6, -14<=k<=14, -26<=l<=26	
Reflections collected	26309	
Independent reflections	3394 [R(int) = 0.0366]	
Completeness to theta = 67.684°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.68979	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3394 / 1 / 240	
Goodness-of-fit on F^2	1.124	
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.1039	
R indices (all data)	R1 = 0.0475, wR2 = 0.1050	
Absolute structure parameter	0.05(6)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.232 and -0.262 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for s16sel2. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8447(6)	7547(3)	2237(2)	24(1)
C(2)	8056(8)	7088(3)	1208(2)	39(1)
C(3)	10189(10)	7018(4)	980(3)	69(2)
C(4)	6545(11)	7223(4)	698(2)	74(2)
C(5)	7786(5)	6328(3)	2223(1)	18(1)
C(6)	9349(5)	5537(3)	2541(2)	20(1)
C(7)	8280(5)	4812(3)	3035(1)	19(1)
C(8)	6622(5)	4128(3)	2733(2)	24(1)
C(9)	5068(6)	4932(3)	2441(2)	27(1)
C(10)	5750(5)	6134(3)	2529(1)	18(1)
C(11)	6743(5)	5316(3)	4076(1)	20(1)
C(12)	3986(5)	6038(3)	4755(2)	20(1)
C(13)	4937(6)	6560(3)	5254(2)	24(1)
C(14)	3917(6)	6675(3)	5820(2)	28(1)
C(15)	2008(6)	6269(3)	5880(2)	29(1)
C(16)	1079(6)	5743(3)	5378(2)	29(1)
C(17)	2062(6)	5618(3)	4810(2)	26(1)
C(18)	4463(5)	6503(3)	3616(2)	19(1)
N(1)	7446(4)	5608(2)	3486(1)	18(1)
N(2)	5020(4)	5950(2)	4166(1)	21(1)
N(3)	6027(4)	6351(2)	3203(1)	16(1)
O(1)	7791(5)	7976(2)	1647(1)	32(1)
O(2)	7588(4)	6088(2)	1565(1)	23(1)
O(3)	10303(4)	4848(2)	2095(1)	32(1)
O(4)	7505(4)	4661(2)	4439(1)	30(1)
O(5)	2960(4)	7036(2)	3522(1)	30(1)

Table 3. Bond lengths [Å] for s16sel2.

C(1)-O(1)	1.422(4)
C(1)-C(5)	1.527(4)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-O(1)	1.427(4)
C(2)-O(2)	1.453(4)
C(2)-C(4)	1.491(7)
C(2)-C(3)	1.511(7)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(5)-O(2)	1.432(3)
C(5)-C(10)	1.528(4)
C(5)-C(6)	1.566(4)
C(6)-O(3)	1.408(4)
C(6)-C(7)	1.538(4)
C(6)-H(6)	1.0000
C(7)-N(1)	1.462(4)
C(7)-C(8)	1.521(4)
C(7)-H(7)	1.0000
C(8)-C(9)	1.548(5)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.522(5)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-N(3)	1.467(4)
C(10)-H(10)	1.0000
C(11)-O(4)	1.214(4)
C(11)-N(1)	1.382(4)
C(11)-N(2)	1.395(4)
C(12)-C(13)	1.385(5)
C(12)-C(17)	1.389(5)
C(12)-N(2)	1.433(4)

C(13)-C(14)	1.388(5)
C(13)-H(13)	0.9500
C(14)-C(15)	1.375(5)
C(14)-H(14)	0.9500
C(15)-C(16)	1.385(5)
C(15)-H(15)	0.9500
C(16)-C(17)	1.382(5)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500
C(18)-O(5)	1.209(4)
C(18)-N(3)	1.377(4)
C(18)-N(2)	1.395(4)
N(1)-N(3)	1.434(4)
O(3)-H(3)	0.84(2)

Table 4. Bond angles [°] for s16sel2.

O(1)-C(1)-C(5)	103.9(3)
O(1)-C(1)-H(1A)	111.0
C(5)-C(1)-H(1A)	111.0
O(1)-C(1)-H(1B)	111.0
C(5)-C(1)-H(1B)	111.0
H(1A)-C(1)-H(1B)	109.0
O(1)-C(2)-O(2)	104.2(3)
O(1)-C(2)-C(4)	108.1(4)
O(2)-C(2)-C(4)	108.8(4)
O(1)-C(2)-C(3)	111.6(4)
O(2)-C(2)-C(3)	109.0(4)
C(4)-C(2)-C(3)	114.6(4)
C(2)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(2)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
C(2)-C(4)-H(4A)	109.5
C(2)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(2)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
O(2)-C(5)-C(1)	103.7(2)
O(2)-C(5)-C(10)	107.5(3)
C(1)-C(5)-C(10)	113.4(3)
O(2)-C(5)-C(6)	111.1(3)
C(1)-C(5)-C(6)	112.2(3)
C(10)-C(5)-C(6)	108.7(2)
O(3)-C(6)-C(7)	109.8(3)
O(3)-C(6)-C(5)	111.7(3)
C(7)-C(6)-C(5)	108.9(3)
O(3)-C(6)-H(6)	108.8
C(7)-C(6)-H(6)	108.8
C(5)-C(6)-H(6)	108.8
N(1)-C(7)-C(8)	110.4(3)

N(1)-C(7)-C(6)	104.9(2)
C(8)-C(7)-C(6)	110.9(3)
N(1)-C(7)-H(7)	110.2
C(8)-C(7)-H(7)	110.2
C(6)-C(7)-H(7)	110.2
C(7)-C(8)-C(9)	108.9(3)
C(7)-C(8)-H(8A)	109.9
C(9)-C(8)-H(8A)	109.9
C(7)-C(8)-H(8B)	109.9
C(9)-C(8)-H(8B)	109.9
H(8A)-C(8)-H(8B)	108.3
C(10)-C(9)-C(8)	109.7(3)
C(10)-C(9)-H(9A)	109.7
C(8)-C(9)-H(9A)	109.7
C(10)-C(9)-H(9B)	109.7
C(8)-C(9)-H(9B)	109.7
H(9A)-C(9)-H(9B)	108.2
N(3)-C(10)-C(9)	109.0(3)
N(3)-C(10)-C(5)	105.9(2)
C(9)-C(10)-C(5)	111.1(3)
N(3)-C(10)-H(10)	110.2
C(9)-C(10)-H(10)	110.2
C(5)-C(10)-H(10)	110.2
O(4)-C(11)-N(1)	126.6(3)
O(4)-C(11)-N(2)	127.8(3)
N(1)-C(11)-N(2)	105.6(3)
C(13)-C(12)-C(17)	121.8(3)
C(13)-C(12)-N(2)	118.6(3)
C(17)-C(12)-N(2)	119.6(3)
C(12)-C(13)-C(14)	118.6(3)
C(12)-C(13)-H(13)	120.7
C(14)-C(13)-H(13)	120.7
C(15)-C(14)-C(13)	120.2(3)
C(15)-C(14)-H(14)	119.9
C(13)-C(14)-H(14)	119.9
C(14)-C(15)-C(16)	120.5(3)
C(14)-C(15)-H(15)	119.7
C(16)-C(15)-H(15)	119.7
C(17)-C(16)-C(15)	120.4(3)

C(17)-C(16)-H(16)	119.8
C(15)-C(16)-H(16)	119.8
C(16)-C(17)-C(12)	118.4(3)
C(16)-C(17)-H(17)	120.8
C(12)-C(17)-H(17)	120.8
O(5)-C(18)-N(3)	126.8(3)
O(5)-C(18)-N(2)	127.7(3)
N(3)-C(18)-N(2)	105.5(3)
C(11)-N(1)-N(3)	108.0(3)
C(11)-N(1)-C(7)	124.0(3)
N(3)-N(1)-C(7)	112.6(2)
C(11)-N(2)-C(18)	111.3(3)
C(11)-N(2)-C(12)	124.1(3)
C(18)-N(2)-C(12)	124.6(3)
C(18)-N(3)-N(1)	108.7(2)
C(18)-N(3)-C(10)	123.2(3)
N(1)-N(3)-C(10)	112.4(2)
C(1)-O(1)-C(2)	105.5(3)
C(5)-O(2)-C(2)	108.9(2)
C(6)-O(3)-H(3)	112(3)

Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for s16sel2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	32(2)	17(2)	25(2)	-1(1)	4(2)	-3(1)
C(2)	76(3)	20(2)	21(2)	3(1)	15(2)	2(2)
C(3)	105(5)	34(2)	67(3)	-3(2)	58(4)	-11(3)
C(4)	163(7)	38(3)	21(2)	0(2)	-29(3)	23(3)
C(5)	24(2)	16(1)	14(1)	-2(1)	0(1)	0(1)
C(6)	17(2)	23(2)	22(2)	-2(1)	-1(1)	1(1)
C(7)	19(2)	18(2)	18(1)	-3(1)	1(1)	3(1)
C(8)	30(2)	17(2)	25(2)	-3(1)	0(1)	-4(1)
C(9)	31(2)	26(2)	26(2)	1(1)	-7(2)	-7(2)
C(10)	19(2)	21(2)	12(1)	-1(1)	-4(1)	2(1)
C(11)	20(2)	22(2)	17(1)	-2(1)	-2(1)	0(1)
C(12)	23(2)	21(2)	15(1)	2(1)	1(1)	1(1)
C(13)	25(2)	26(2)	21(2)	1(1)	-2(2)	-4(2)
C(14)	40(2)	26(2)	18(2)	1(1)	-2(2)	-1(2)
C(15)	36(2)	30(2)	20(2)	6(1)	11(2)	1(2)
C(16)	25(2)	32(2)	31(2)	4(2)	8(2)	-6(2)
C(17)	30(2)	28(2)	21(2)	-2(1)	1(1)	0(2)
C(18)	16(2)	25(2)	17(2)	0(1)	0(1)	1(1)
N(1)	19(1)	19(1)	15(1)	0(1)	-3(1)	7(1)
N(2)	24(1)	25(1)	14(1)	1(1)	1(1)	3(1)
N(3)	14(1)	20(1)	12(1)	1(1)	0(1)	5(1)
O(1)	56(2)	16(1)	22(1)	3(1)	12(1)	4(1)
O(2)	36(1)	21(1)	12(1)	-1(1)	2(1)	0(1)
O(3)	38(2)	37(1)	22(1)	-2(1)	7(1)	15(1)
O(4)	39(2)	33(1)	19(1)	7(1)	-2(1)	9(1)
O(5)	23(1)	42(1)	24(1)	6(1)	3(1)	14(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for s16sel2.

	x	y	z	U(eq)
H(1A)	7812	7951	2590	29
H(1B)	9915	7606	2277	29
H(3A)	11084	6933	1342	103
H(3B)	10530	7702	751	103
H(3C)	10336	6374	699	103
H(4A)	5201	7200	880	111
H(4B)	6691	6616	391	111
H(4C)	6748	7941	486	111
H(6)	10380	6002	2758	24
H(7)	9258	4309	3249	22
H(8A)	5975	3652	3054	29
H(8B)	7185	3639	2402	29
H(9A)	4915	4769	1986	33
H(9B)	3756	4823	2647	33
H(10)	4740	6659	2349	21
H(13)	6261	6834	5210	28
H(14)	4541	7035	6166	34
H(15)	1319	6350	6268	35
H(16)	-241	5466	5425	35
H(17)	1436	5253	4465	32
H(3)	9930(70)	4990(40)	1728(14)	48

Table 7. Torsion angles [°] for s16sel2.

O(1)-C(1)-C(5)-O(2)	22.6(3)
O(1)-C(1)-C(5)-C(10)	-93.7(3)
O(1)-C(1)-C(5)-C(6)	142.6(3)
O(2)-C(5)-C(6)-O(3)	5.0(4)
C(1)-C(5)-C(6)-O(3)	-110.6(3)
C(10)-C(5)-C(6)-O(3)	123.2(3)
O(2)-C(5)-C(6)-C(7)	-116.4(3)
C(1)-C(5)-C(6)-C(7)	128.1(3)
C(10)-C(5)-C(6)-C(7)	1.8(3)
O(3)-C(6)-C(7)-N(1)	177.0(3)
C(5)-C(6)-C(7)-N(1)	-60.4(3)
O(3)-C(6)-C(7)-C(8)	-63.8(3)
C(5)-C(6)-C(7)-C(8)	58.7(3)
N(1)-C(7)-C(8)-C(9)	54.7(3)
C(6)-C(7)-C(8)-C(9)	-61.1(3)
C(7)-C(8)-C(9)-C(10)	2.2(4)
C(8)-C(9)-C(10)-N(3)	-57.7(4)
C(8)-C(9)-C(10)-C(5)	58.7(4)
O(2)-C(5)-C(10)-N(3)	178.2(2)
C(1)-C(5)-C(10)-N(3)	-67.8(3)
C(6)-C(5)-C(10)-N(3)	57.8(3)
O(2)-C(5)-C(10)-C(9)	59.9(3)
C(1)-C(5)-C(10)-C(9)	174.0(3)
C(6)-C(5)-C(10)-C(9)	-60.5(3)
C(17)-C(12)-C(13)-C(14)	-0.9(5)
N(2)-C(12)-C(13)-C(14)	178.2(3)
C(12)-C(13)-C(14)-C(15)	0.5(5)
C(13)-C(14)-C(15)-C(16)	-0.1(6)
C(14)-C(15)-C(16)-C(17)	0.0(6)
C(15)-C(16)-C(17)-C(12)	-0.4(5)
C(13)-C(12)-C(17)-C(16)	0.9(5)
N(2)-C(12)-C(17)-C(16)	-178.2(3)
O(4)-C(11)-N(1)-N(3)	176.4(3)
N(2)-C(11)-N(1)-N(3)	-4.9(3)
O(4)-C(11)-N(1)-C(7)	41.5(5)
N(2)-C(11)-N(1)-C(7)	-139.9(3)
C(8)-C(7)-N(1)-C(11)	75.2(4)

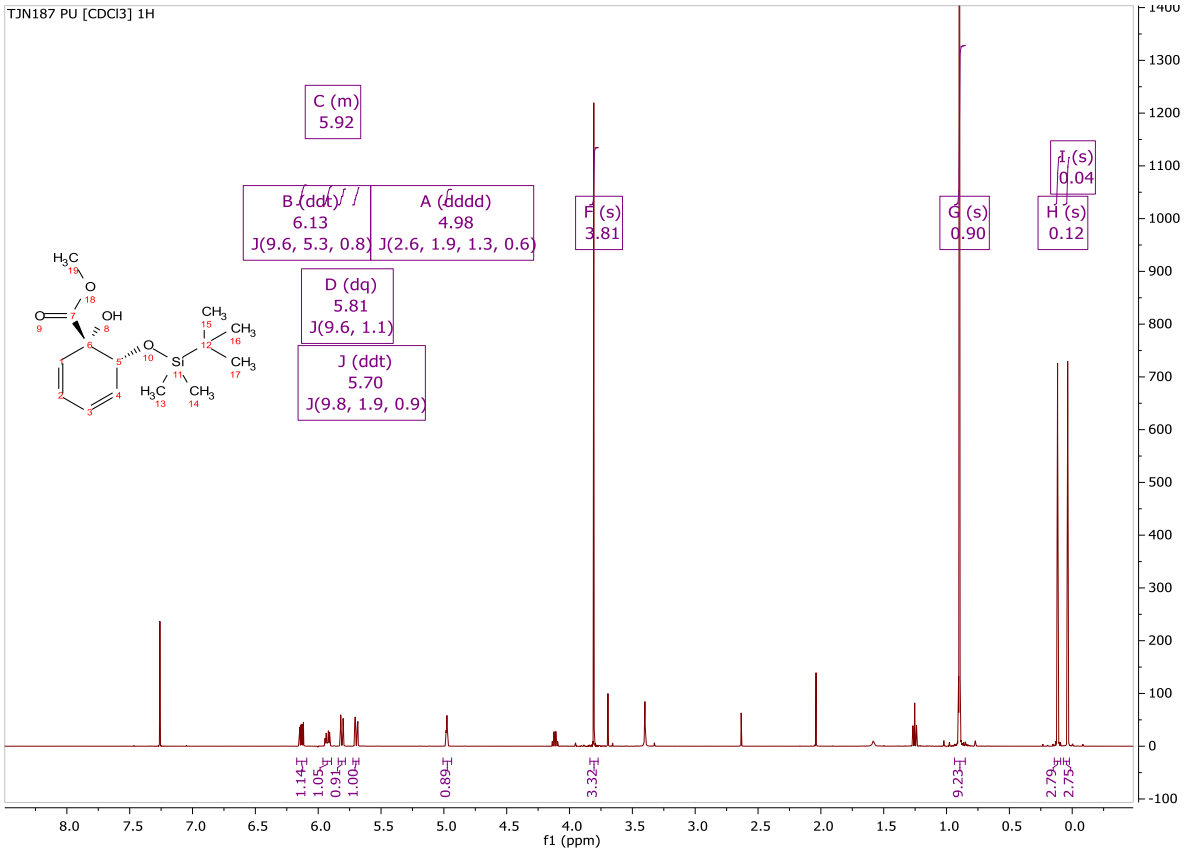
C(6)-C(7)-N(1)-C(11)	-165.3(3)
C(8)-C(7)-N(1)-N(3)	-58.0(3)
C(6)-C(7)-N(1)-N(3)	61.5(3)
O(4)-C(11)-N(2)-C(18)	-172.5(3)
N(1)-C(11)-N(2)-C(18)	8.8(4)
O(4)-C(11)-N(2)-C(12)	8.8(5)
N(1)-C(11)-N(2)-C(12)	-169.8(3)
O(5)-C(18)-N(2)-C(11)	173.0(3)
N(3)-C(18)-N(2)-C(11)	-9.2(4)
O(5)-C(18)-N(2)-C(12)	-8.3(6)
N(3)-C(18)-N(2)-C(12)	169.5(3)
C(13)-C(12)-N(2)-C(11)	65.8(4)
C(17)-C(12)-N(2)-C(11)	-115.0(4)
C(13)-C(12)-N(2)-C(18)	-112.6(4)
C(17)-C(12)-N(2)-C(18)	66.5(5)
O(5)-C(18)-N(3)-N(1)	-176.4(3)
N(2)-C(18)-N(3)-N(1)	5.8(3)
O(5)-C(18)-N(3)-C(10)	-41.8(5)
N(2)-C(18)-N(3)-C(10)	140.4(3)
C(11)-N(1)-N(3)-C(18)	-0.6(3)
C(7)-N(1)-N(3)-C(18)	140.0(3)
C(11)-N(1)-N(3)-C(10)	-140.4(3)
C(7)-N(1)-N(3)-C(10)	0.1(4)
C(9)-C(10)-N(3)-C(18)	-75.1(4)
C(5)-C(10)-N(3)-C(18)	165.3(3)
C(9)-C(10)-N(3)-N(1)	58.1(3)
C(5)-C(10)-N(3)-N(1)	-61.5(3)
C(5)-C(1)-O(1)-C(2)	-36.3(4)
O(2)-C(2)-O(1)-C(1)	35.8(4)
C(4)-C(2)-O(1)-C(1)	151.5(4)
C(3)-C(2)-O(1)-C(1)	-81.7(4)
C(1)-C(5)-O(2)-C(2)	-1.0(4)
C(10)-C(5)-O(2)-C(2)	119.4(3)
C(6)-C(5)-O(2)-C(2)	-121.7(3)
O(1)-C(2)-O(2)-C(5)	-20.9(4)
C(4)-C(2)-O(2)-C(5)	-136.0(4)
C(3)-C(2)-O(2)-C(5)	98.4(4)

Table 8. Hydrogen bonds for s16sel2 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(2)	0.84(2)	2.08(4)	2.604(4)	121(4)

Symmetry transformations used to generate equivalent atoms:

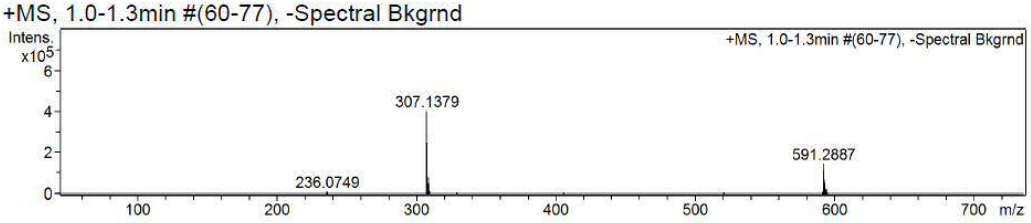
Methyl (1*S*,6*R*)-6-((*tert*-butyldimethylsilyl)oxy)-1-hydroxycyclohexa-2,4-diene-1-carboxylate III-53



Confirmation of Expected Formula

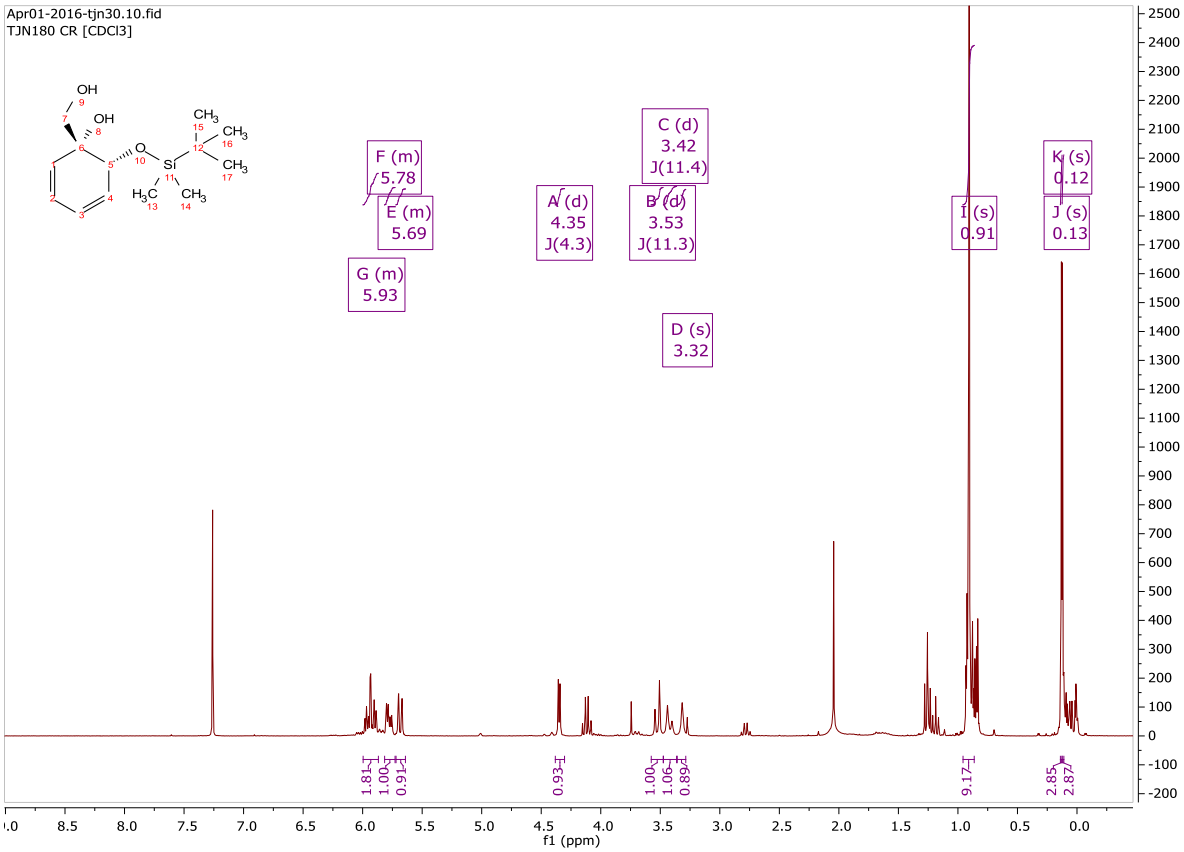
Sample-ID	tn_sel_TJN187	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN187_347304_75_01_52038.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	15/04/2016 14:36:10
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	236.0749	10813	2.7	245	4920.7
2	307.1379	399899	100.0	14093	20576.6
3	308.1341	79810	20.0	4255	4198.2
4	309.1320	20085	5.0	1223	1080.7
5	329.1146	6285	1.6	395	623.6
6	405.1989	5007	1.3	166	1091.8
7	591.2887	145005	36.3	12570	5295.8
8	592.2820	65360	16.3	7303	2435.5
9	593.2797	25730	6.4	3024	978.8
10	594.2789	5593	1.4	505	217.3

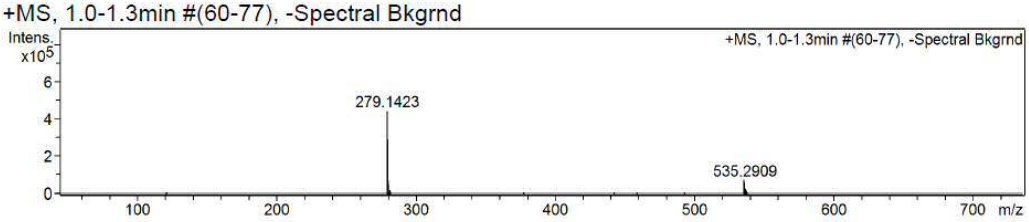
(1*R*,6*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-(hydroxymethyl)cyclohexa-2,4-dien-1-ol III-54



Confirmation of Expected Formula

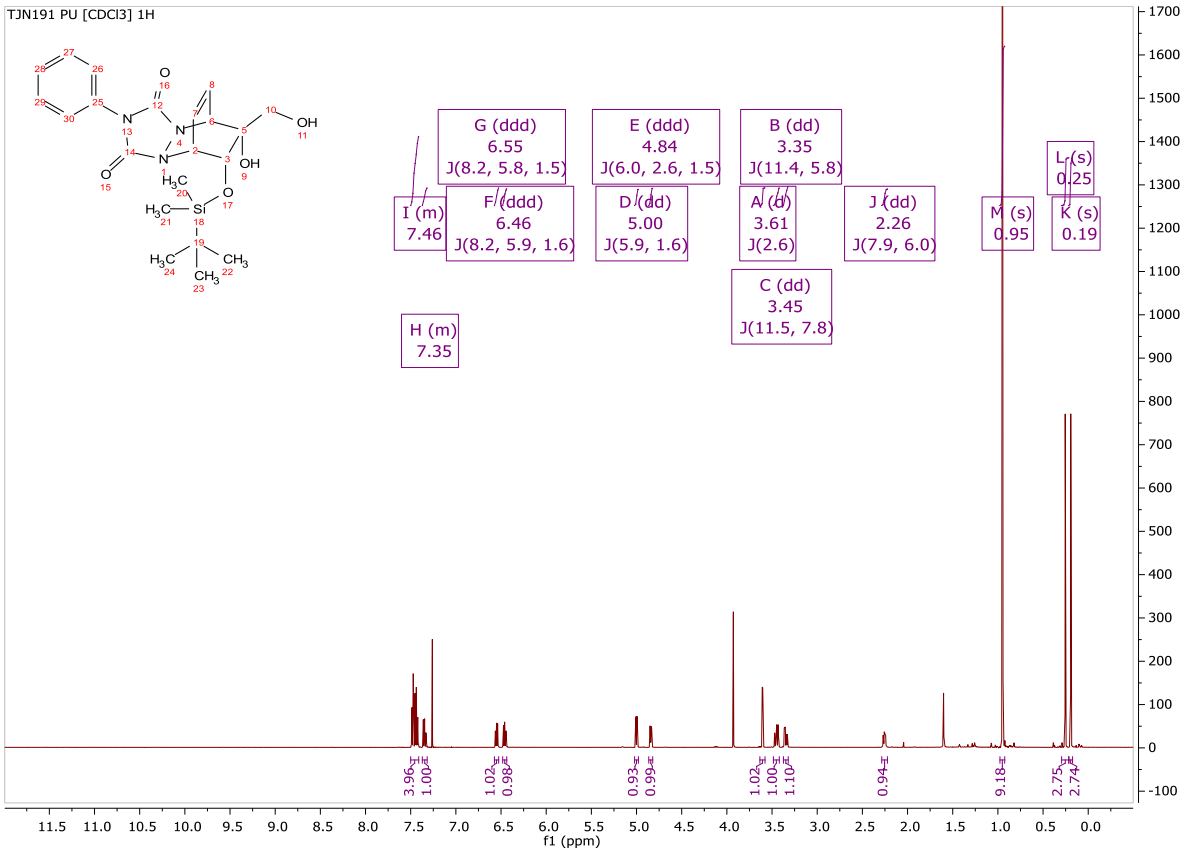
Sample-ID	tn_sel_189	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_189_347370_39_01_52112.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	19/04/2016 15:00:23
Ionisation Mode	positive electrospray (ESI)		

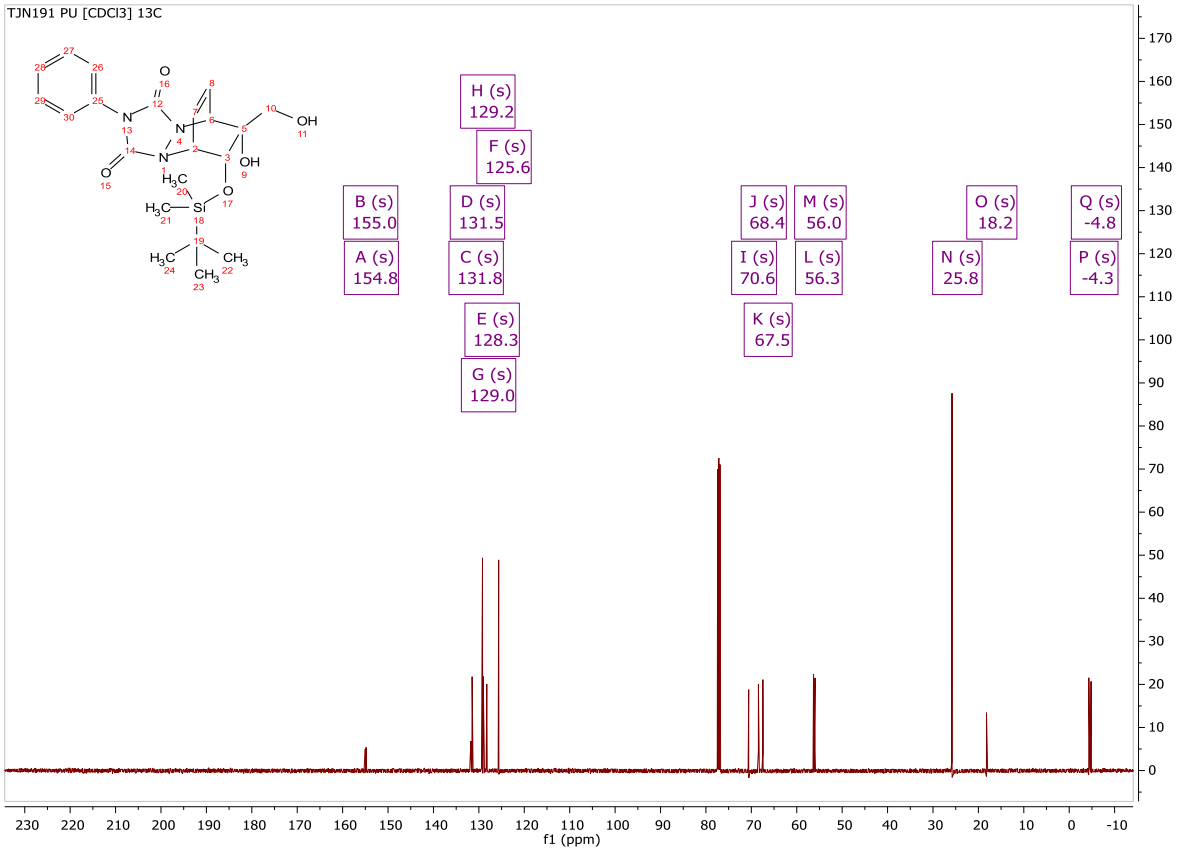
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

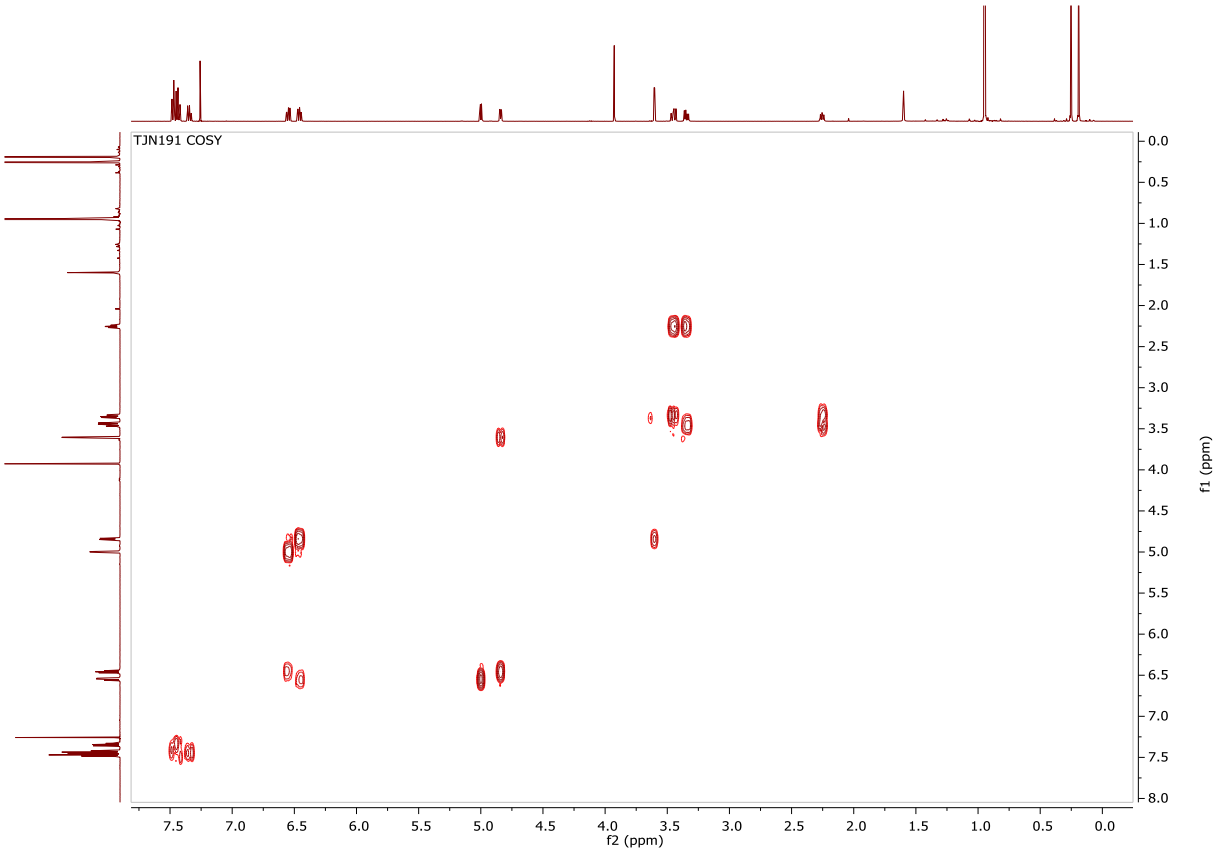


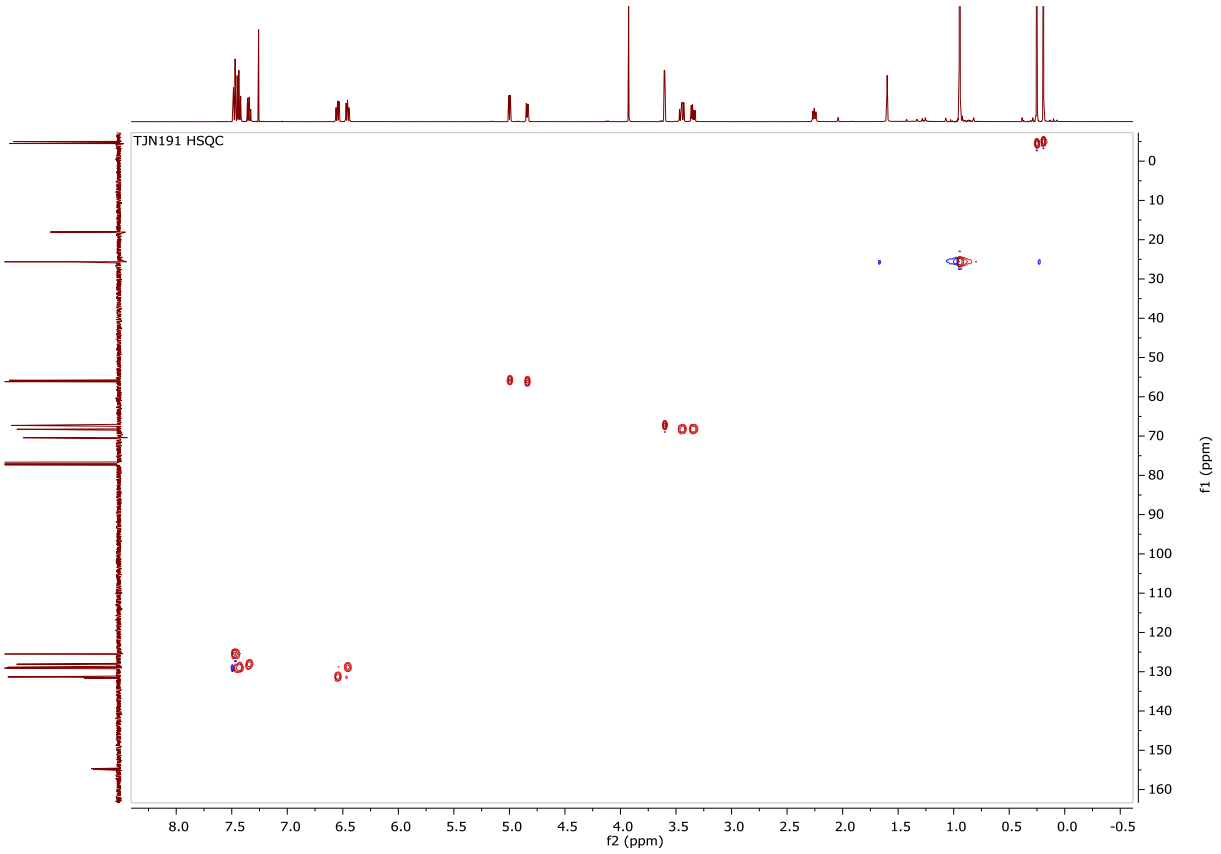
#	m/z	I	I %	Area	S/N
1	279.1423	440079	100.0	14597	24876.4
2	280.1387	71887	16.3	3835	3929.2
3	281.1381	18949	4.3	1130	1002.5
4	377.1333	7232	1.6	514	2885.0
5	442.2398	5222	1.2	494	1116.5
6	458.2333	6869	1.6	667	1292.7
7	492.2199	8724	2.0	823	1105.8
8	535.2909	72175	16.4	7196	5742.9
9	536.2910	29144	6.6	3042	2345.4
10	537.2911	9921	2.3	1079	807.6

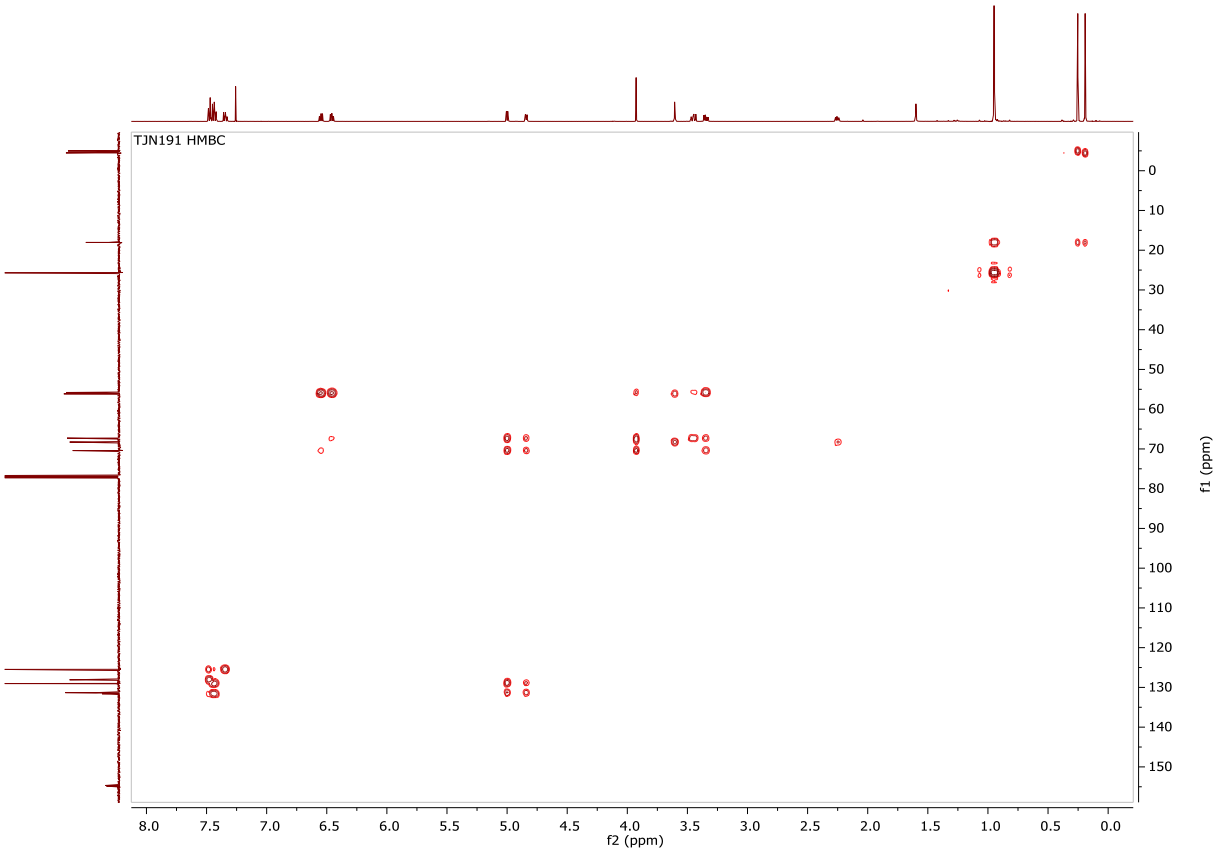
(5*R*,8*S*,10*R*,11*R*)-11-((*tert*-Butyldimethylsilyl)oxy)-10-hydroxy-10-(hydroxymethyl)-2-phenyl-5,8-dihydro-1H-5,8-ethano[1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione III-57






TJN191 COSY
f2 (ppm)
f1 (ppm)

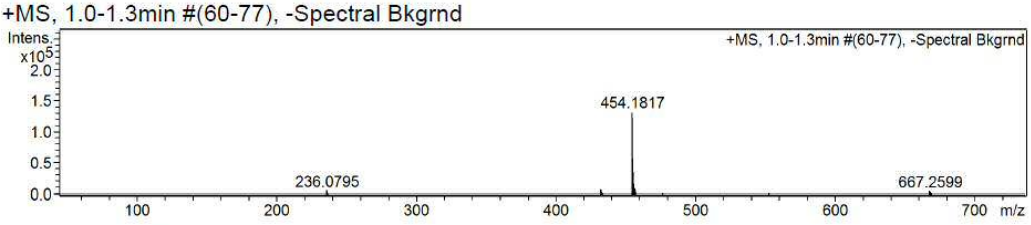

TJN191 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

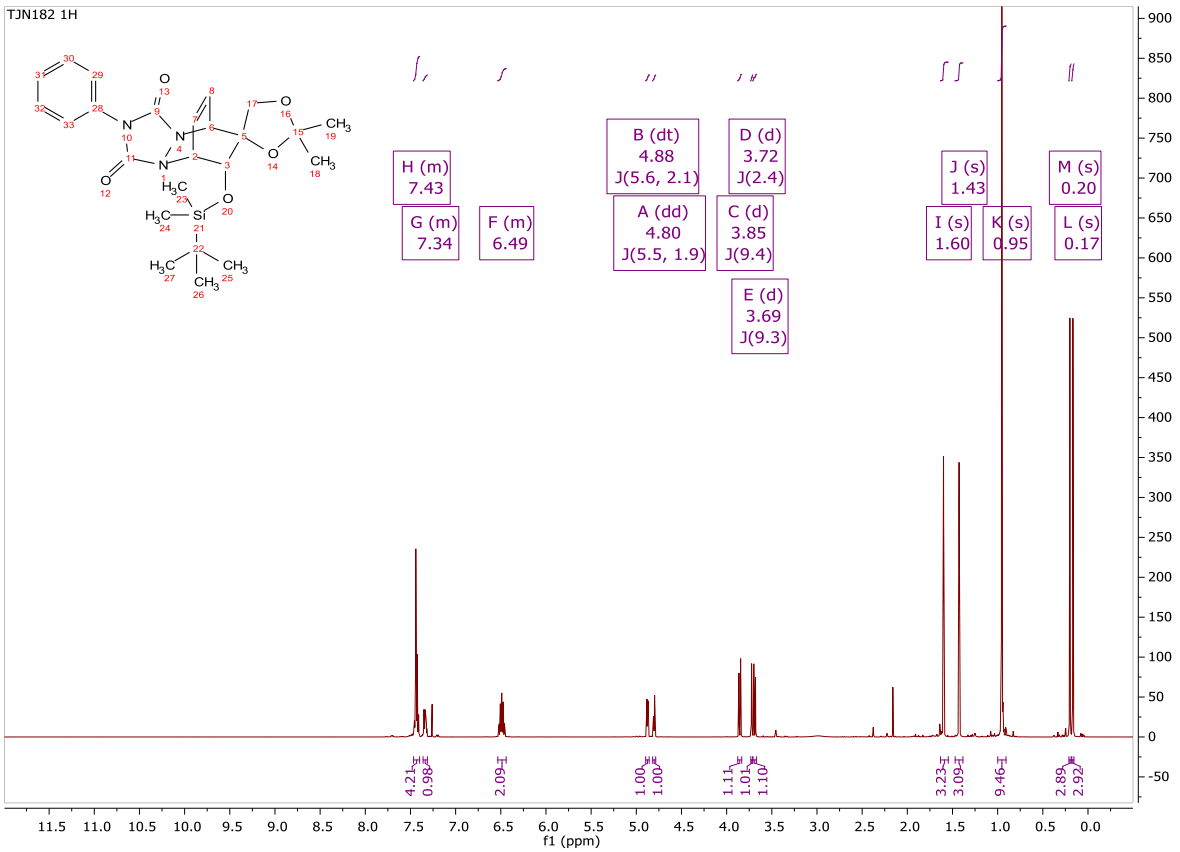
Sample-ID	tn_sel_TJN191	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN191_347525_94_01_52279.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	28/04/2016 17:05:00
Ionisation Mode	positive electrospray (ESI)		

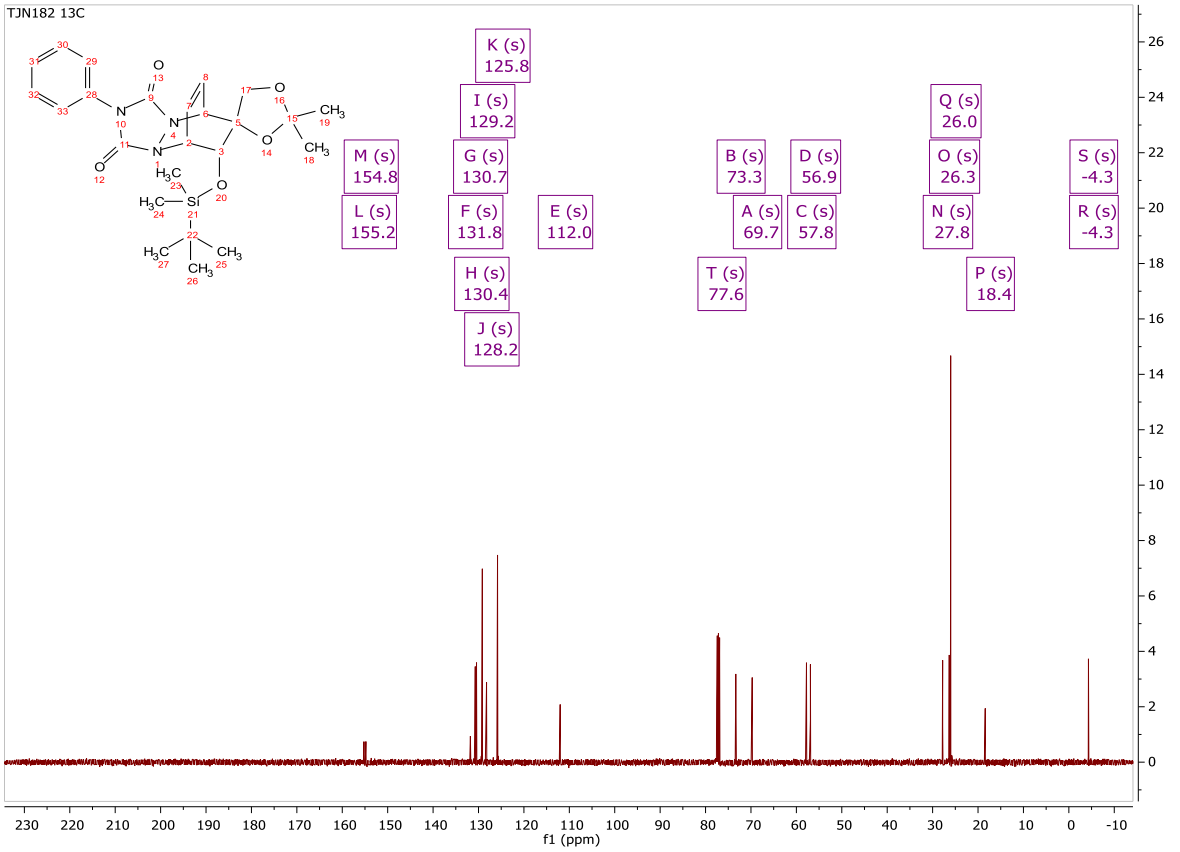
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

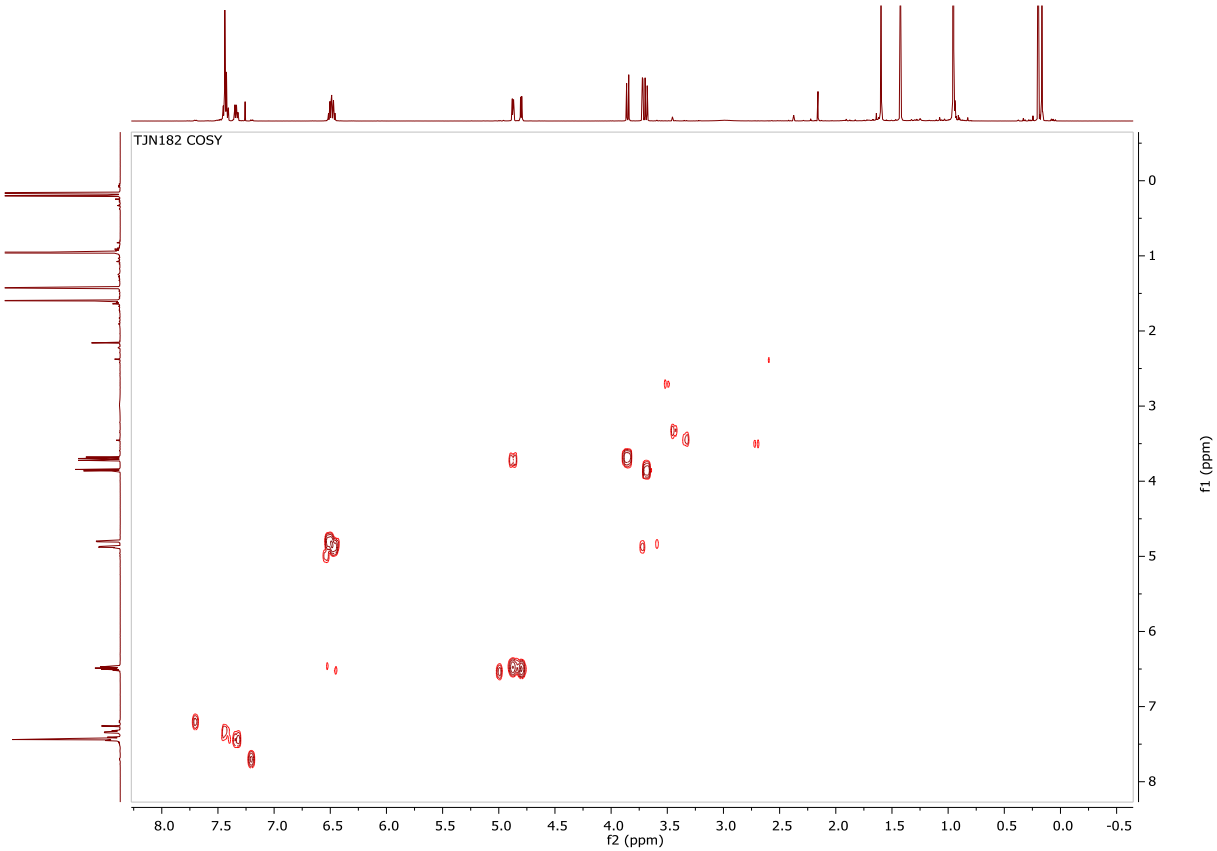


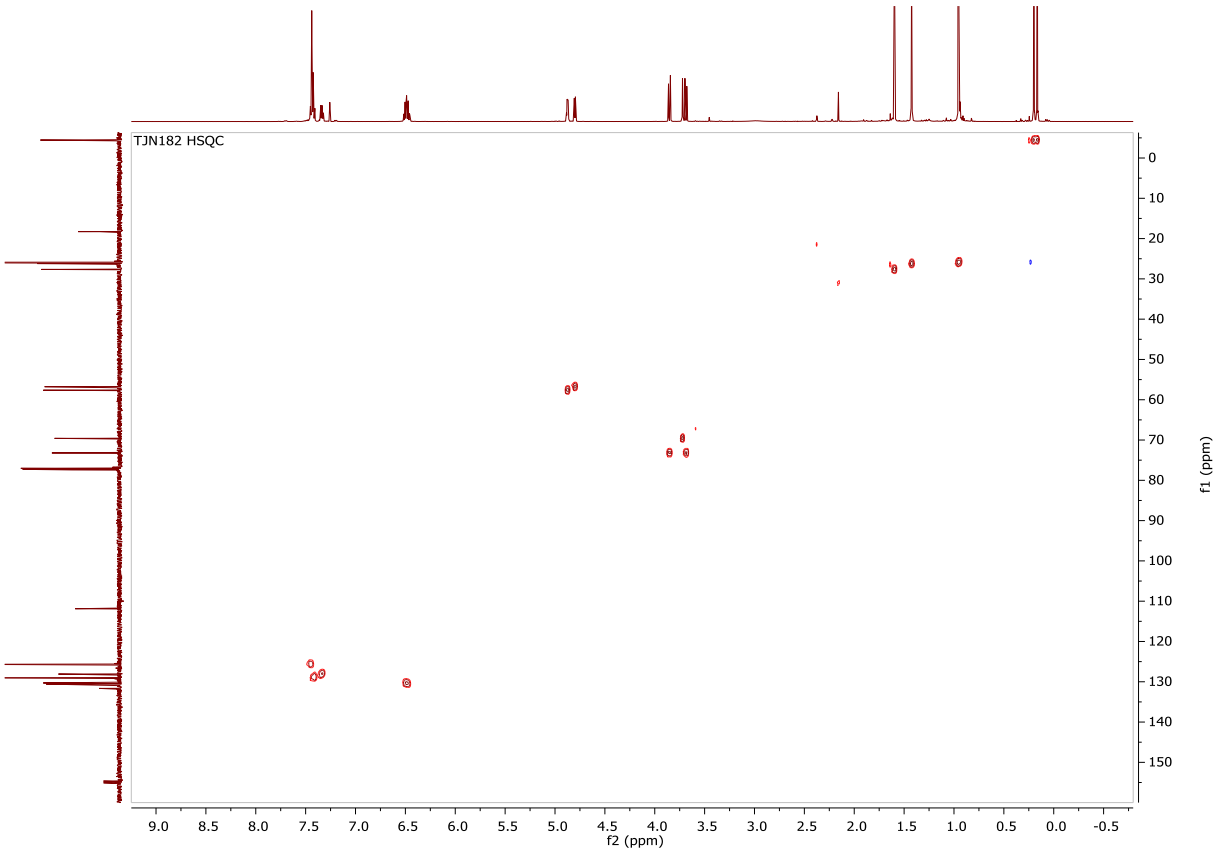
#	m/z	I	I %	Area	S/N
1	236.0795	5613	4.3	220	4714.1
2	432.1979	7786	5.9	699	428.9
3	433.2038	1540	1.2	118	83.0
4	454.1817	131918	100.0	9995	10472.1
5	455.1810	35625	27.0	3386	2919.1
6	456.1803	9934	7.5	917	841.0
7	476.1584	1860	1.4	178	469.7
8	552.1803	1986	1.5	238	1129.1
9	667.2599	4587	3.5	531	1116.4
10	668.2632	1749	1.3	219	429.7

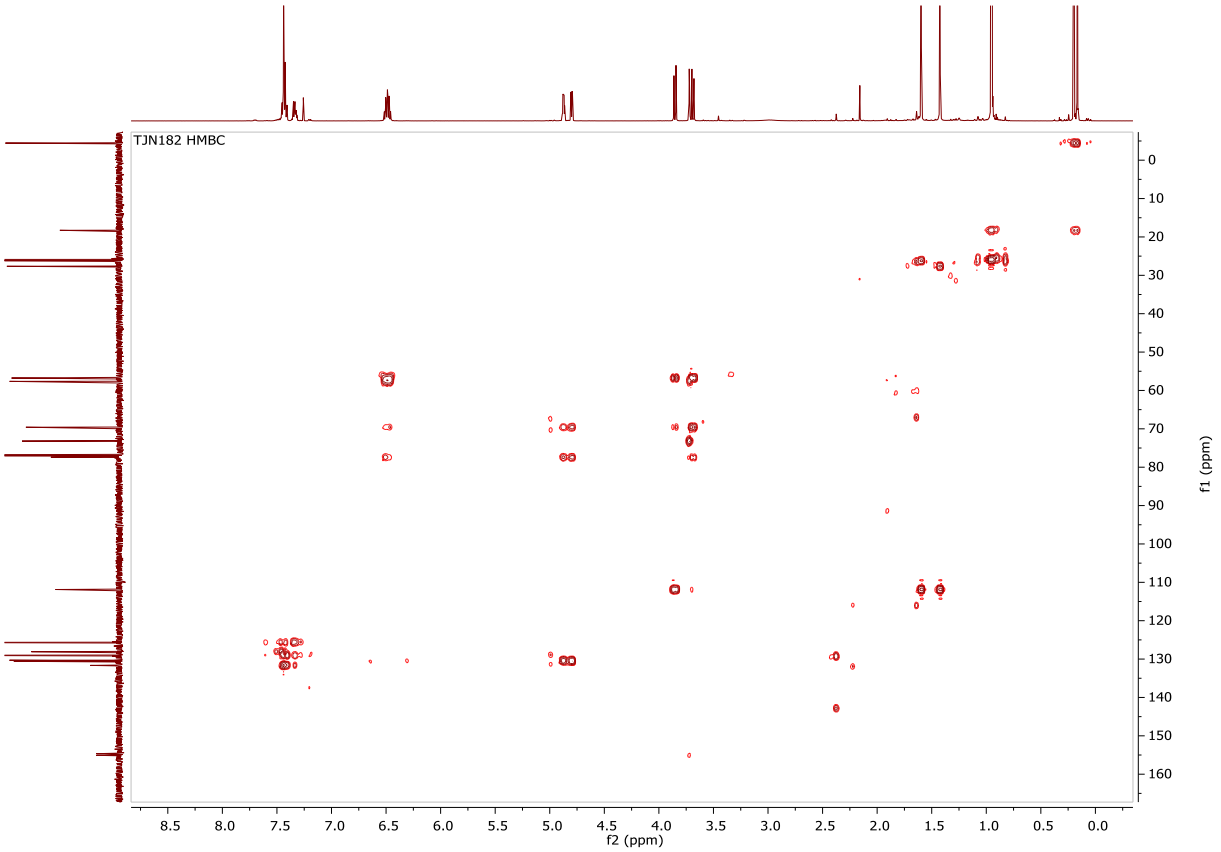
(4*R*,5'*R*,8'*S*,11'*R*)-11'-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-2'-phenyl-5',8'-dihydro-1'H-spiro[[1,3]dioxolane-4,10'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3'(2'H)-dione III-58






TJN182 COSY
f2 (ppm)
f1 (ppm)

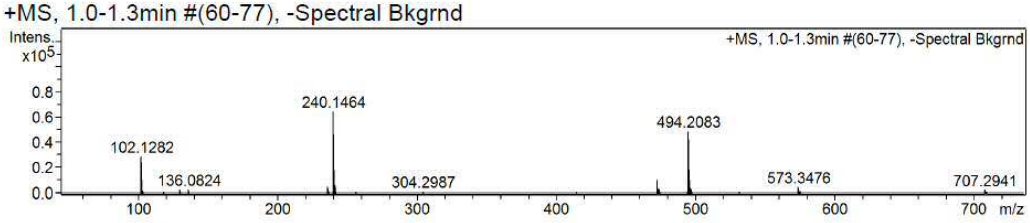

TJN182 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

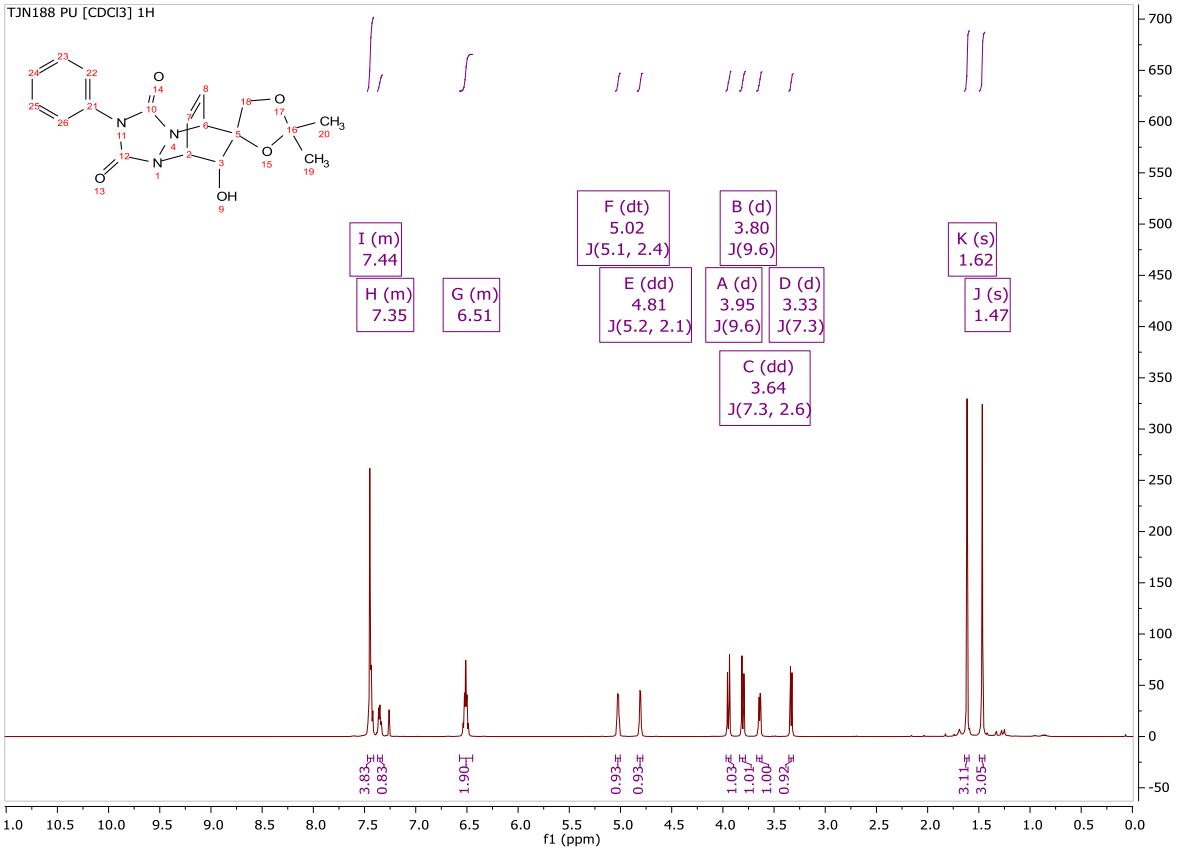
Sample-ID	tn_sel_TJN192	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN192_347621_91_01_52389.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	09/05/2016 11:08:01
Ionisation Mode	positive electrospray (ESI)		

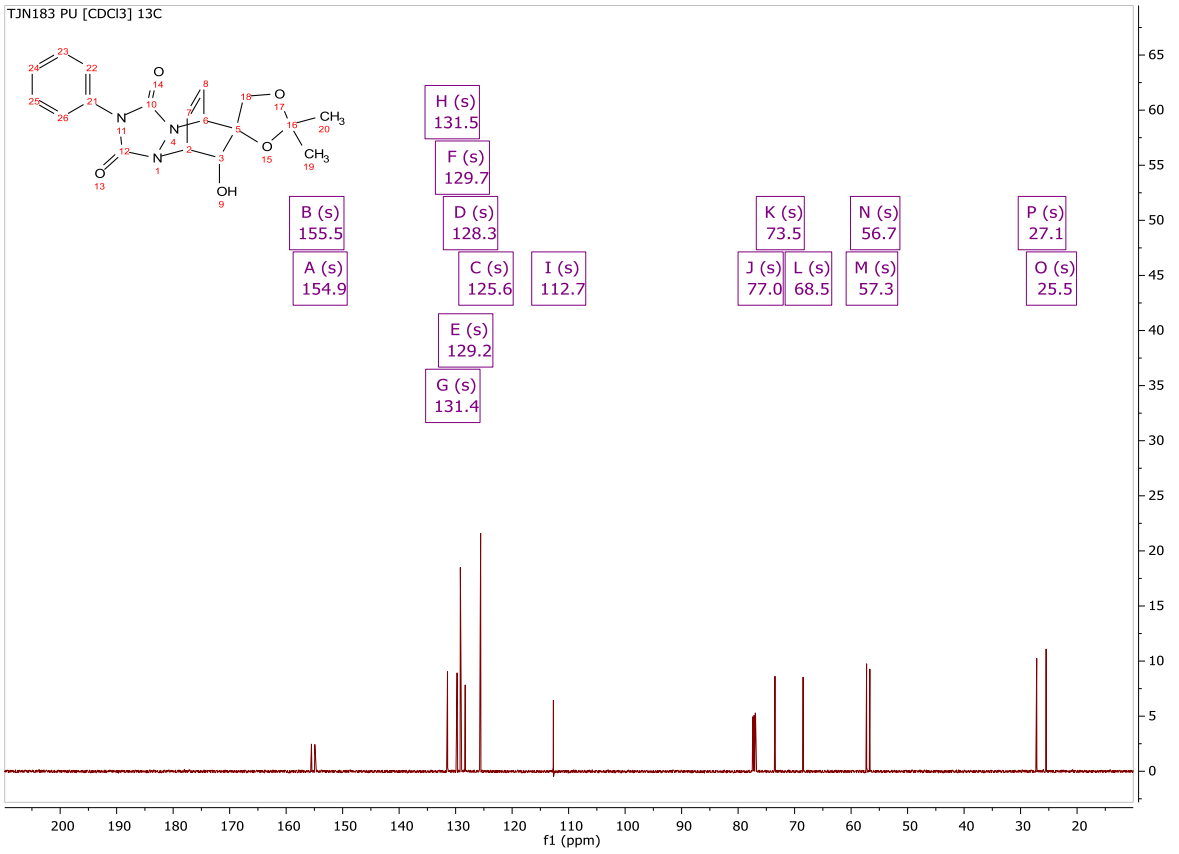
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

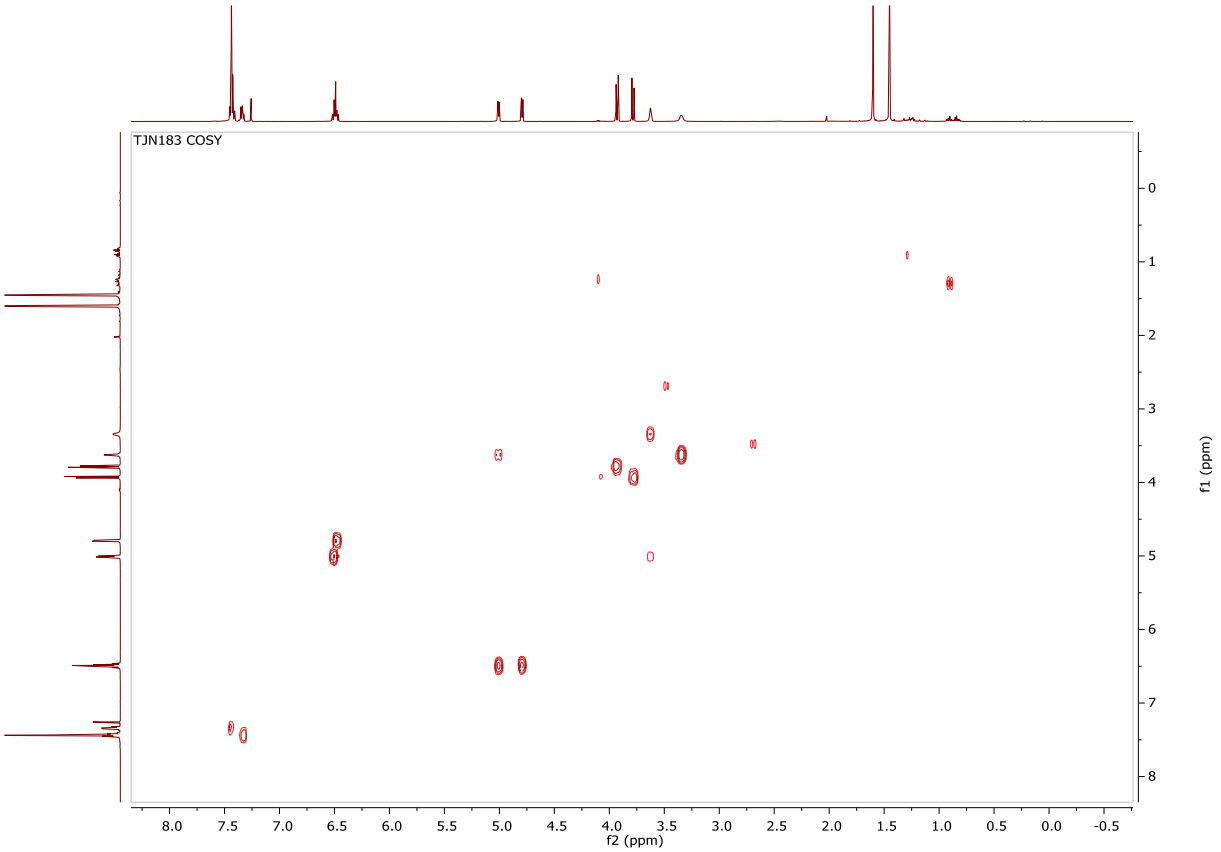


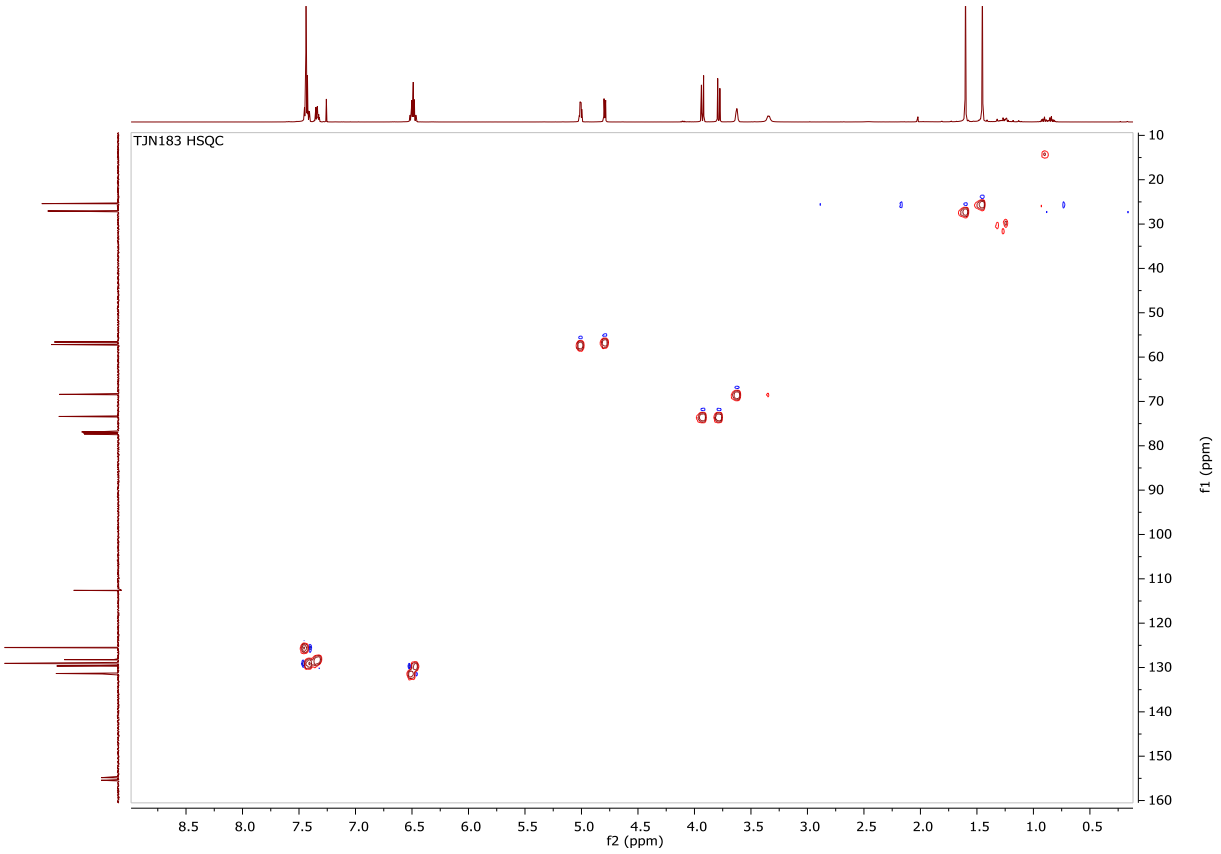
#	m/z	I	I %	Area	S/N
1	102.1282	28655	44.5	364	42952.3
2	136.0824	2638	4.1	36	4552.6
3	240.1464	64342	100.0	1319	8634.0
4	241.1560	6383	9.9	180	833.6
5	472.2264	10571	16.4	1022	946.1
6	473.2314	3266	5.1	315	286.7
7	494.2083	48478	75.3	4364	4541.0
8	495.2110	12529	19.5	1292	1198.1
9	496.2095	3194	5.0	326	311.9
10	573.3476	4664	7.2	569	865.6

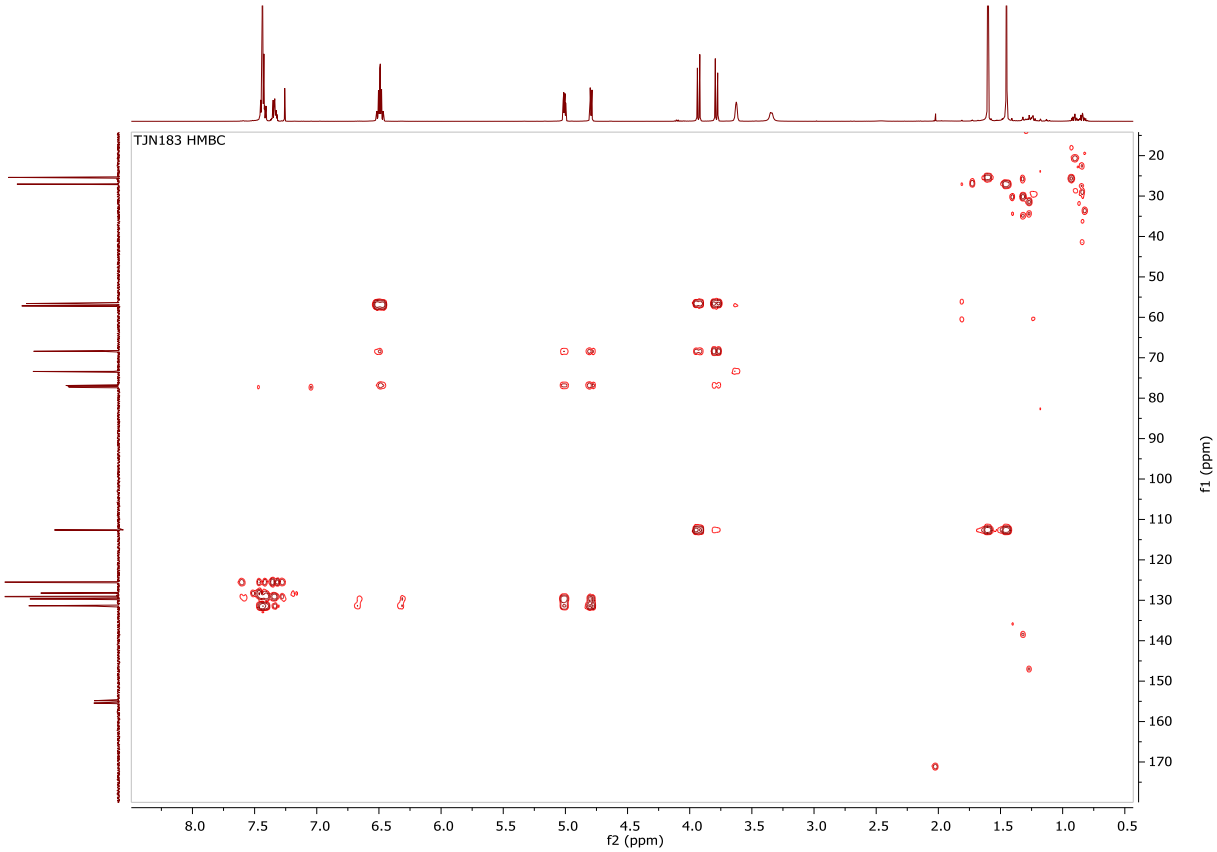
(4*R*,5'*R*,8'*S*,11'*R*)-11'-Hydroxy-2,2-dimethyl-2'-phenyl-5',8'-dihydro-1'H-spiro[[1,3]dioxolane-4,10'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3'(2'H)-dione III-59






TJN183 COSY
f2 (ppm)
f1 (ppm)

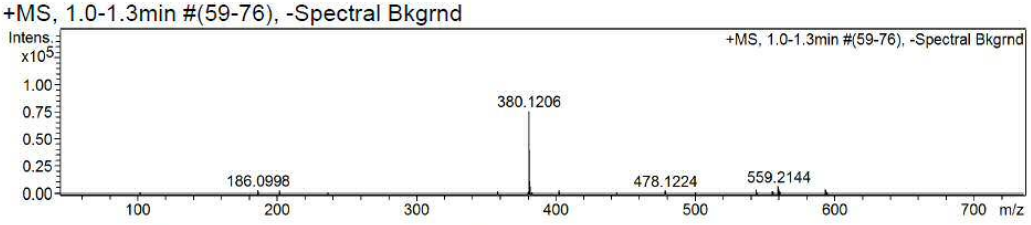

TJN183 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

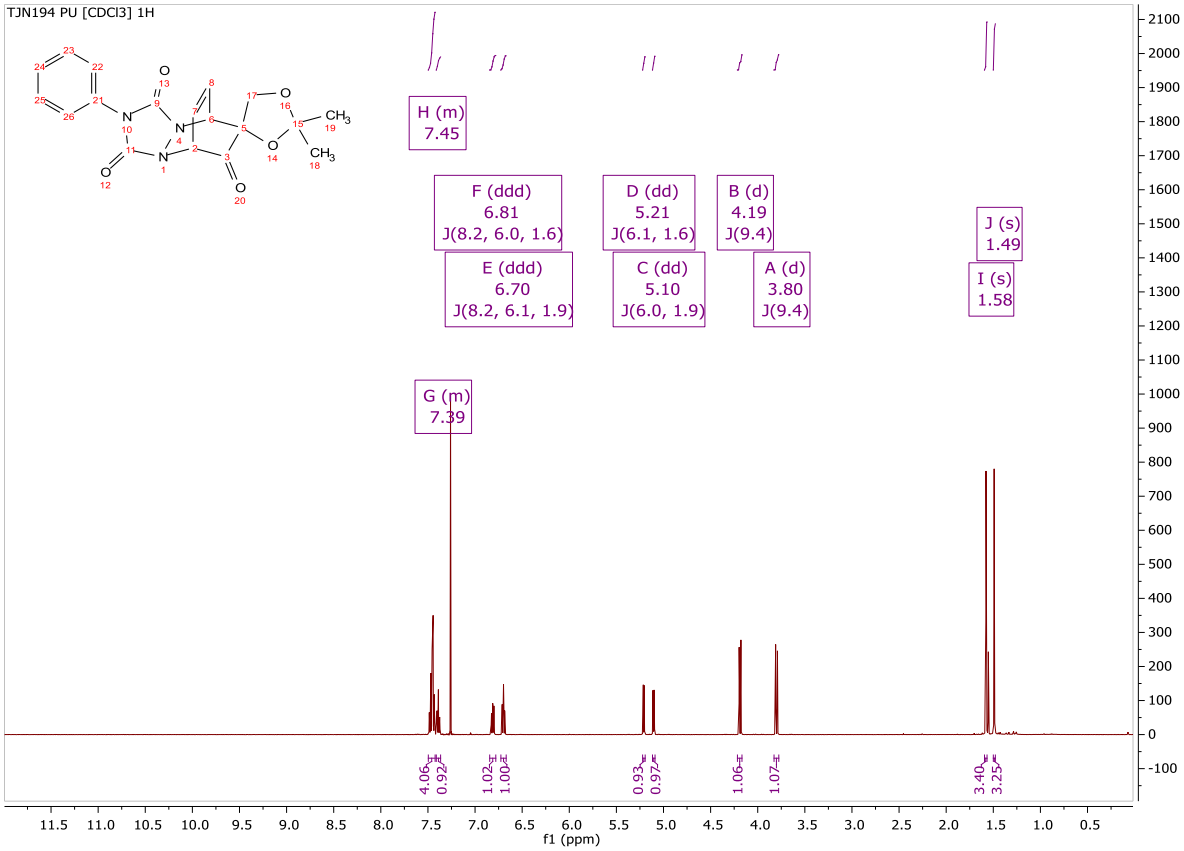
Sample-ID	tn_sel_TJN188	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN188_347369_38_01_52111.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	19/04/2016 14:57:01
Ionisation Mode	positive electrospray (ESI)		

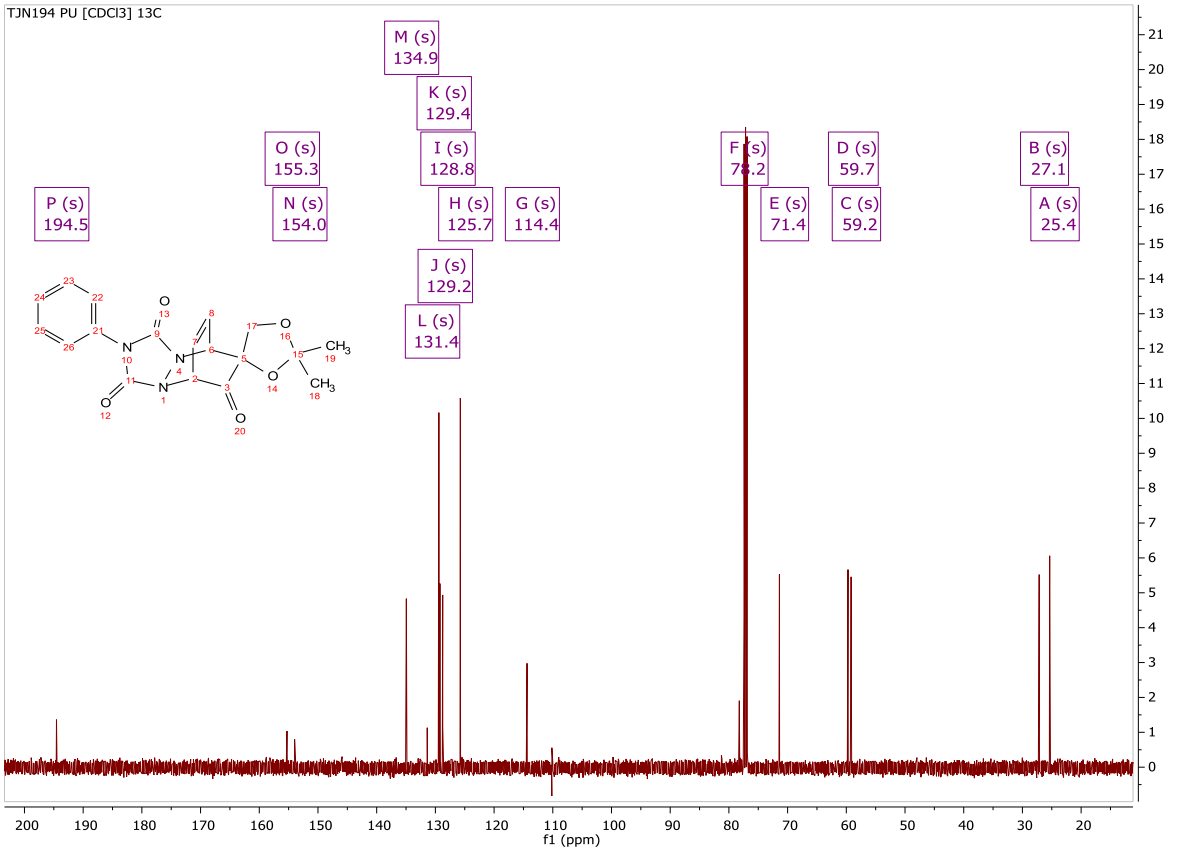
+MS, 1.0-1.3min #(59-76), -Spectral Bkgrnd

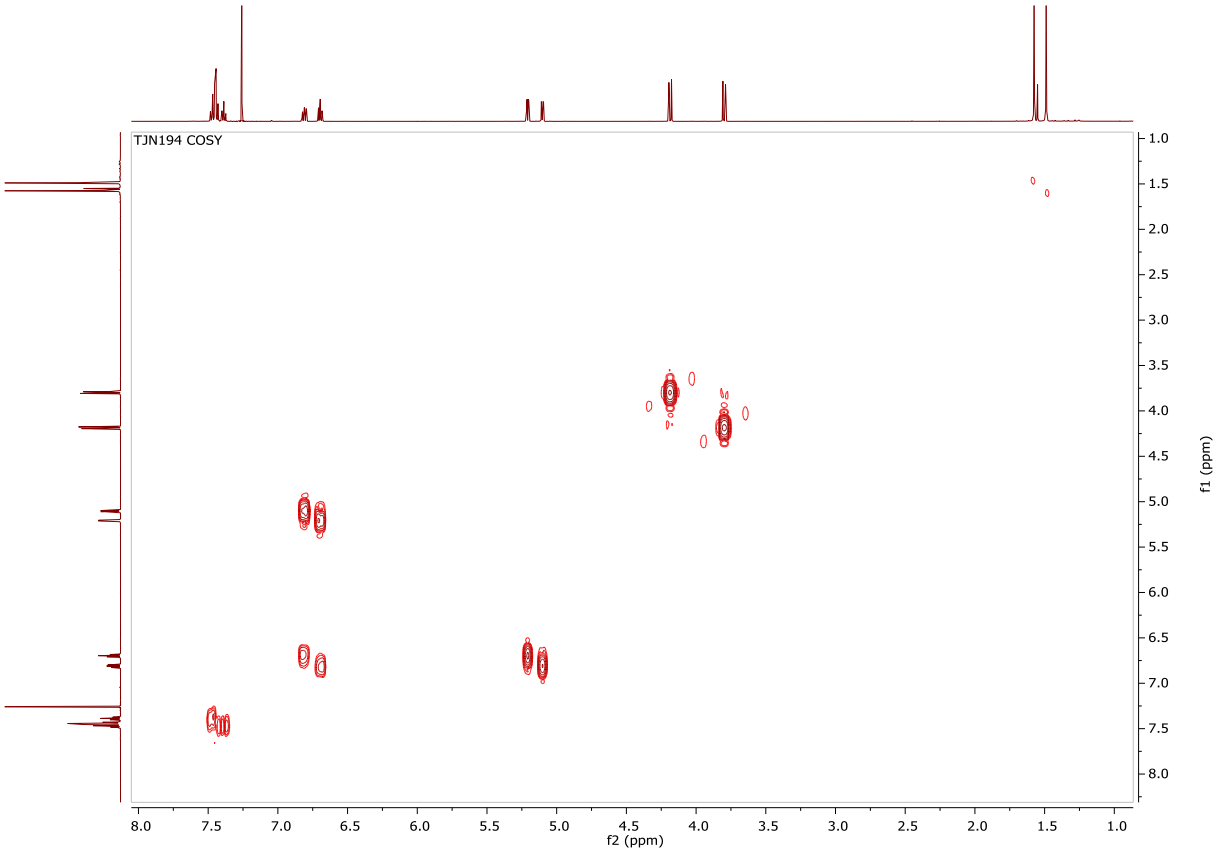


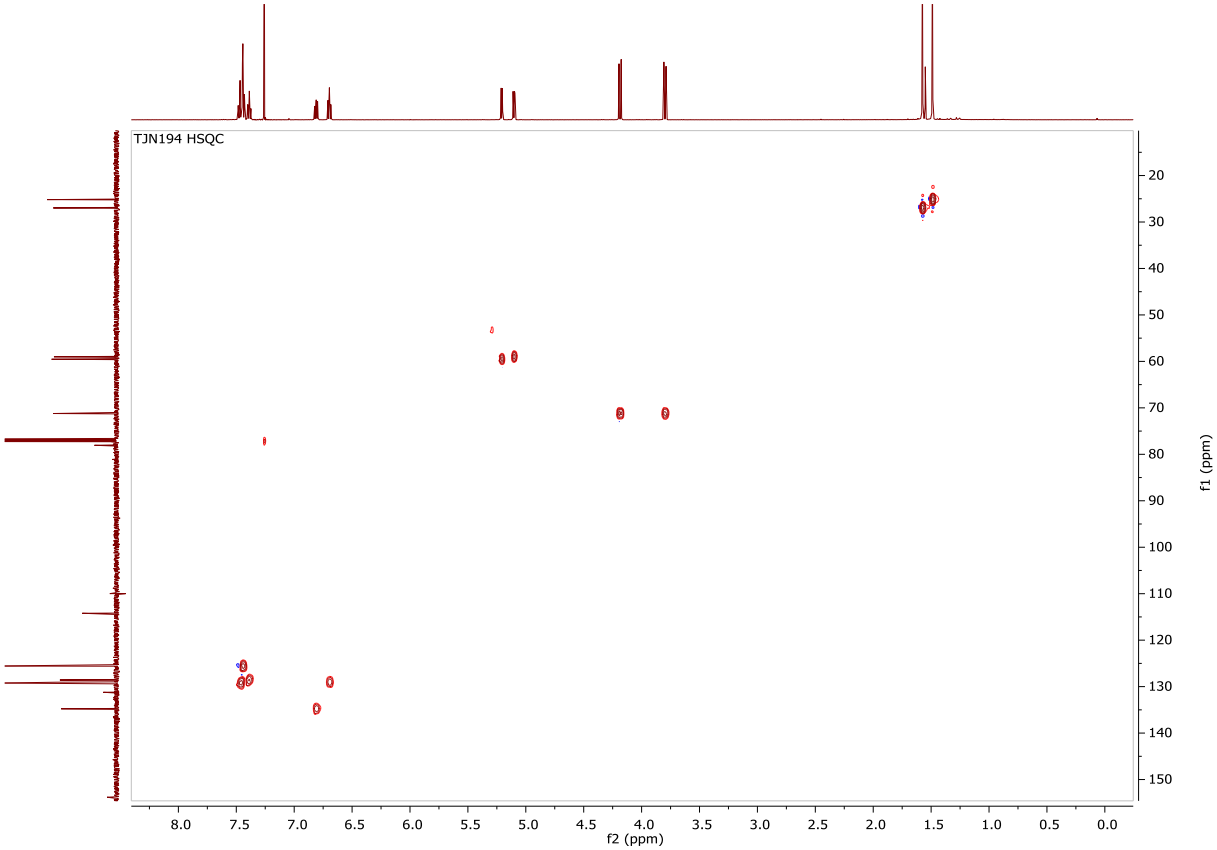
#	m/z	I	I %	Area	S/N
1	186.0998	3023	4.0	40	3510.9
2	202.1038	2574	3.4	67	2118.4
3	358.1387	2227	3.0	166	727.2
4	380.1206	75301	100.0	5436	11836.7
5	381.1244	11889	15.8	866	1825.6
6	402.1032	3059	4.1	242	509.8
7	478.1224	2780	3.7	285	1683.8
8	543.2217	3684	4.9	454	1081.6
9	559.2144	6516	8.7	847	1343.9
10	593.2011	4228	5.6	411	867.1

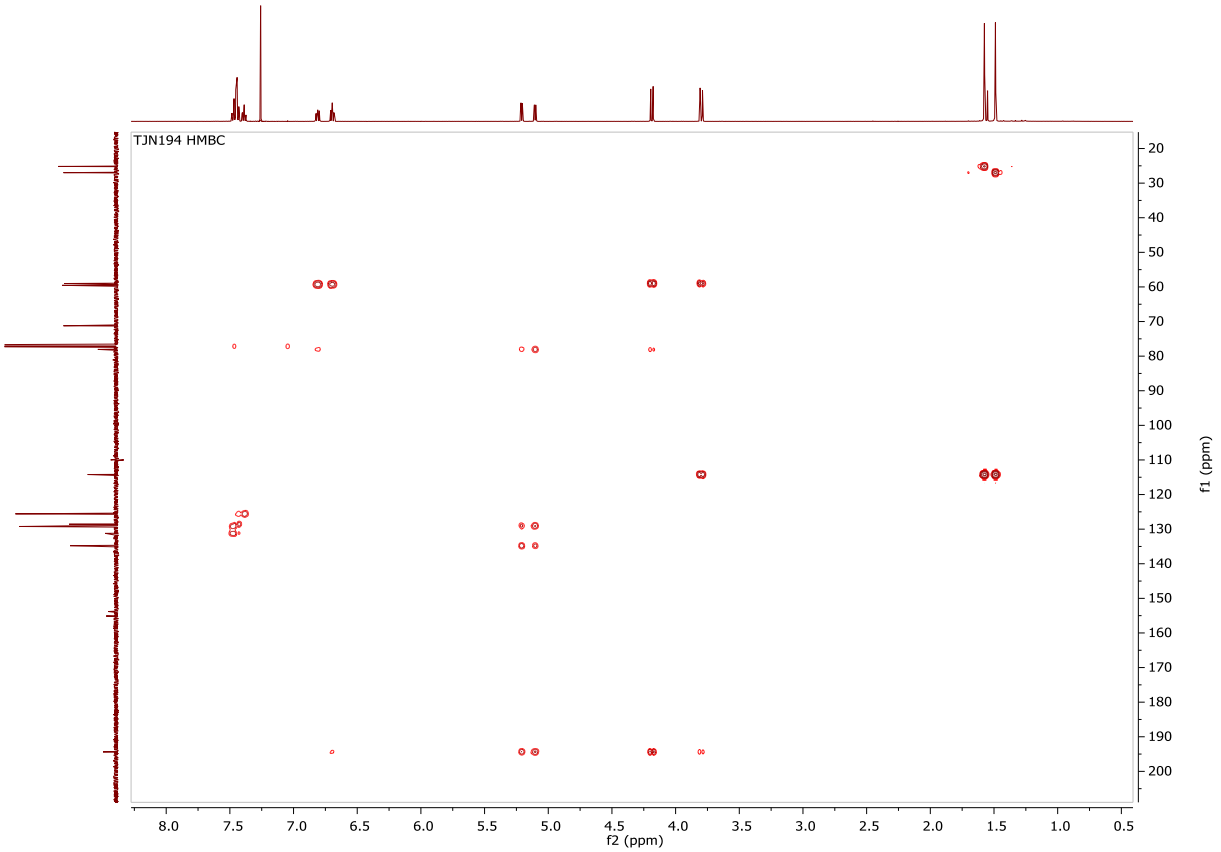
(4*R*,5'*S*,8'*R*)-2,2-Dimethyl-2'-phenyl-5',8'-dihydro-1'H-spiro[[1,3]dioxolane-4,11'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3',10'(2'H)-trione III-60






TJN194 COSY
f2 (ppm)
f1 (ppm)

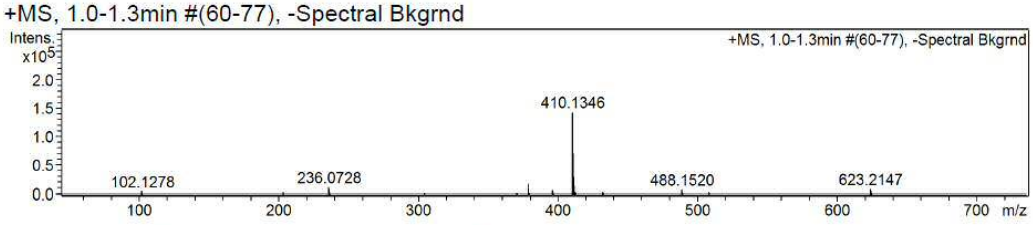

TJN194 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

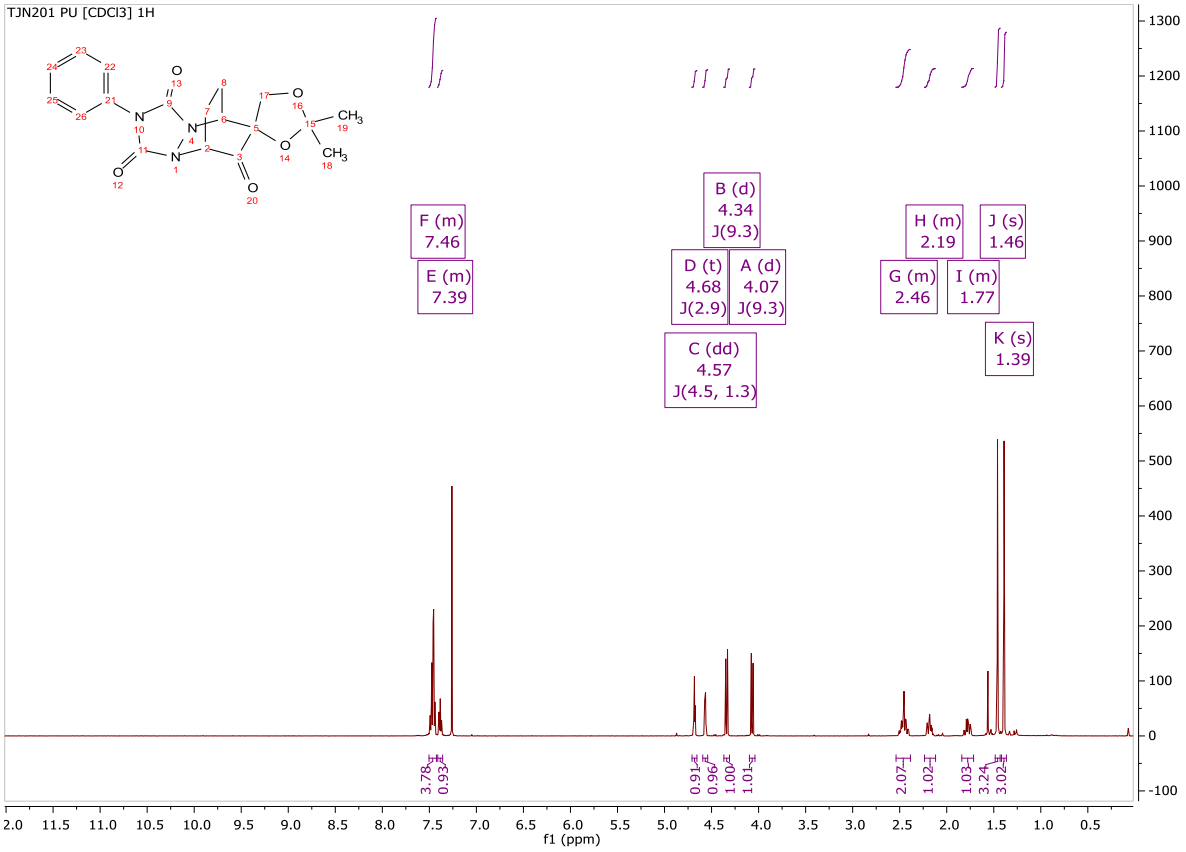
Sample-ID	tn_sel_TJN190 Ketone + hydrate	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN190 Ketone + hydrate__17_01_52198.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	25/04/2016 17:29:11
Ionisation Mode	positive electrospray (ESI)		

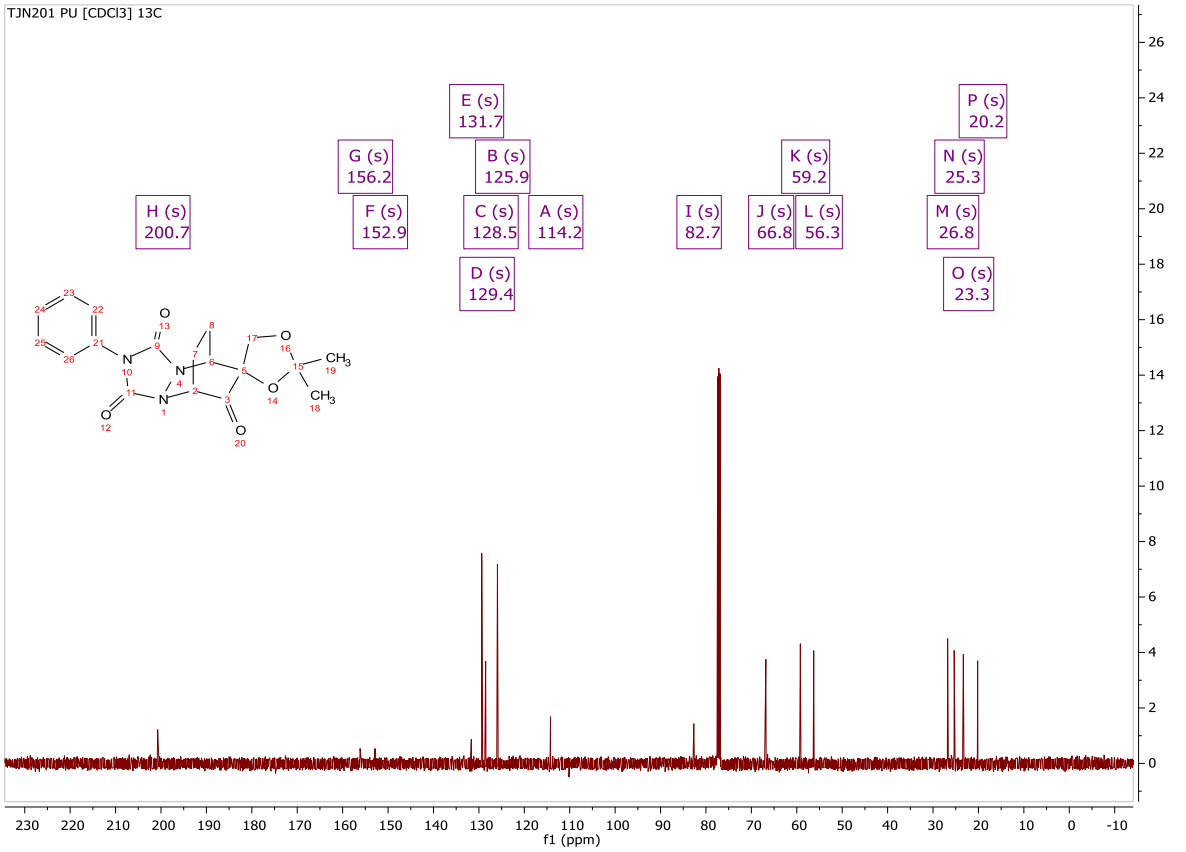
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

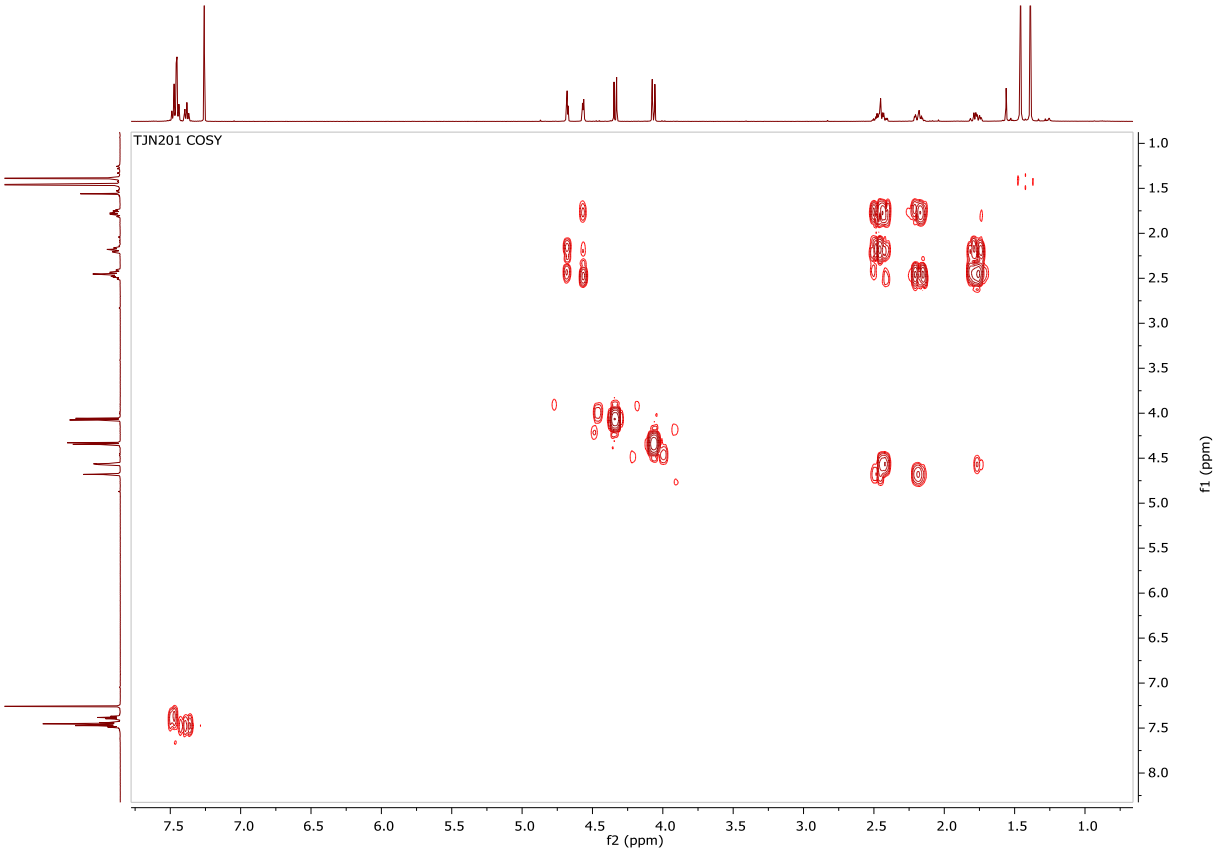


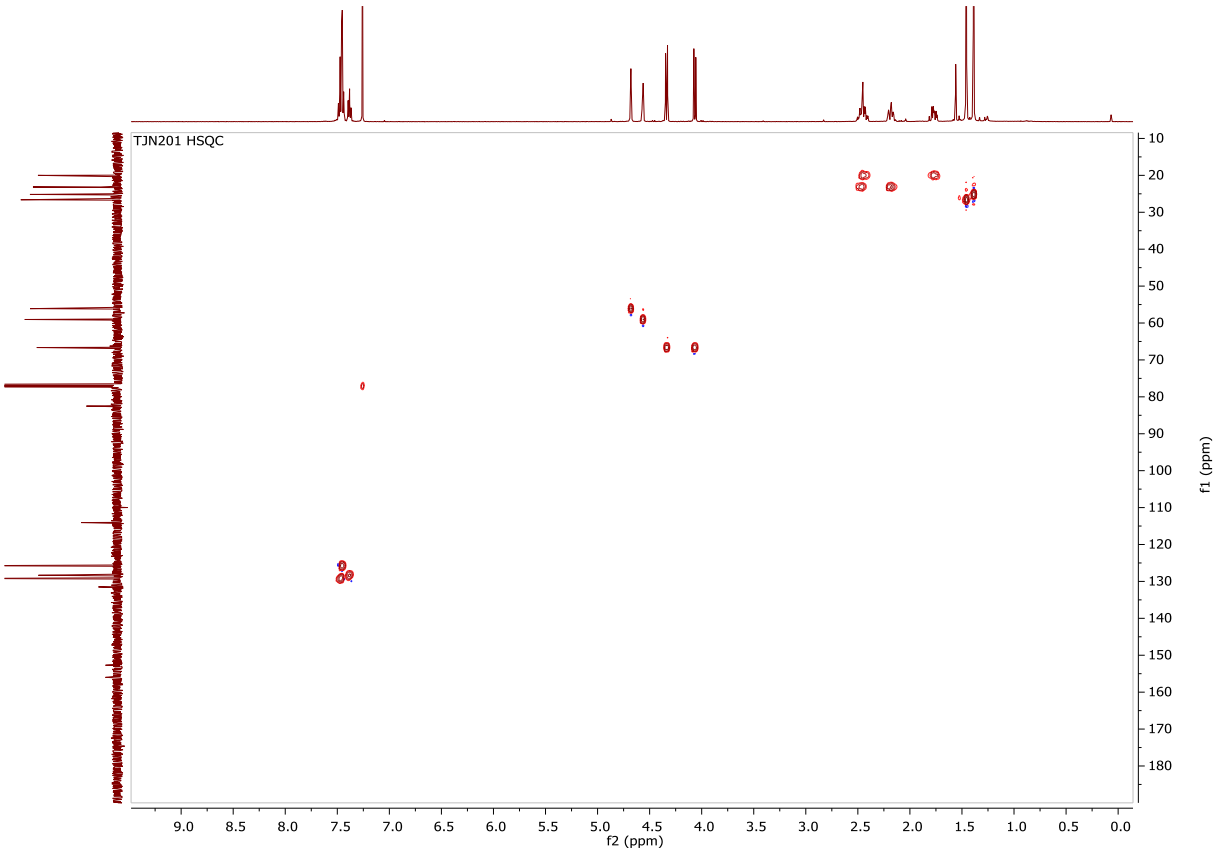
#	m/z	I	I %	Area	S/N
1	102.1278	5410	3.8	94	13302.4
2	236.0728	12494	8.7	276	4427.2
3	378.1067	18004	12.6	1400	916.1
4	396.1185	7640	5.3	620	331.3
5	410.1346	143308	100.0	10060	8606.0
6	411.1362	29671	20.7	2406	1832.2
7	432.1164	4277	3.0	396	648.5
8	488.1520	8598	6.0	932	1109.9
9	508.1346	4192	2.9	456	702.4
10	623.2147	9093	6.3	945	1043.4

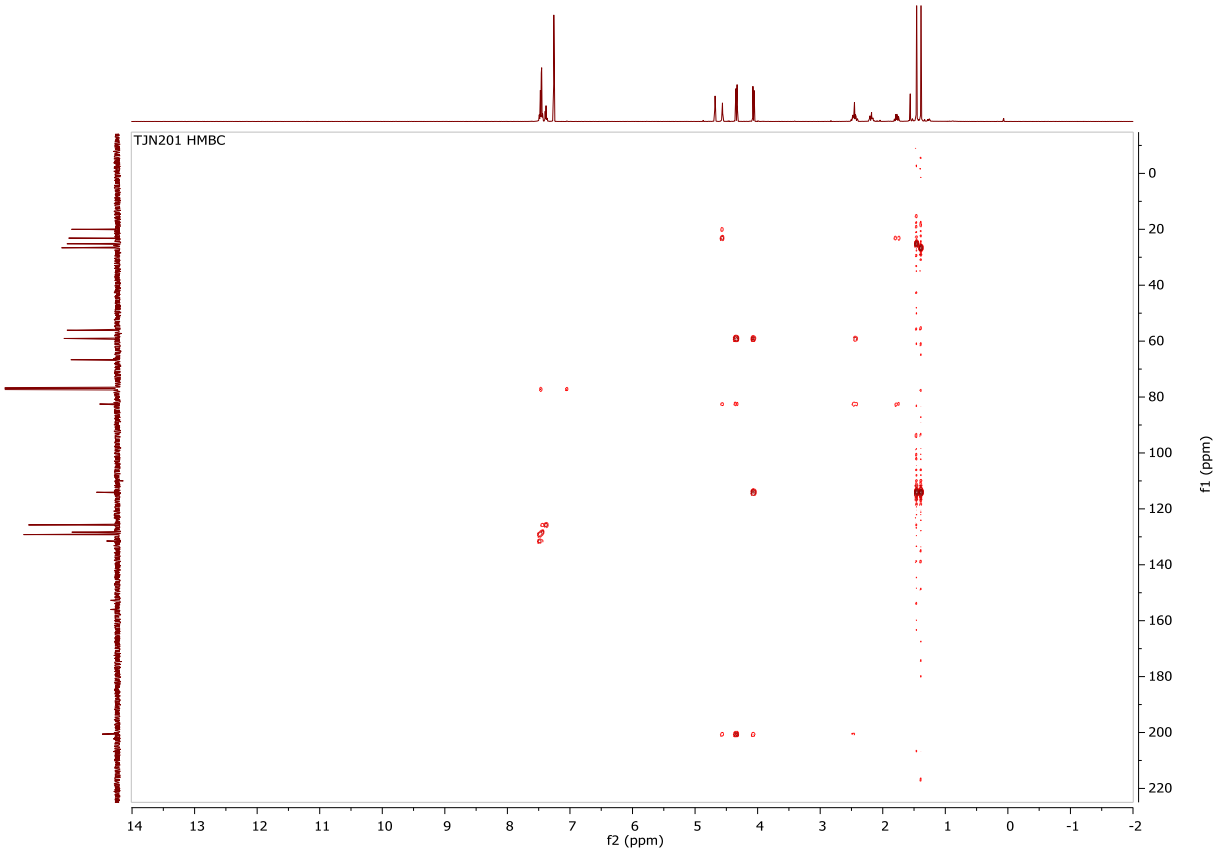
(4*R*,5'*S*,8'*R*)-2,2-Dimethyl-2'-phenyl-1'H,5'H-spiro[[1,3]dioxolane-4,6'-[5,8]ethano[1,2,4]triazolo[1,2-a]pyridazine]-1',3',7'(2'H,8'H)-trione III-41b






TJN201 COSY
f2 (ppm)
f1 (ppm)

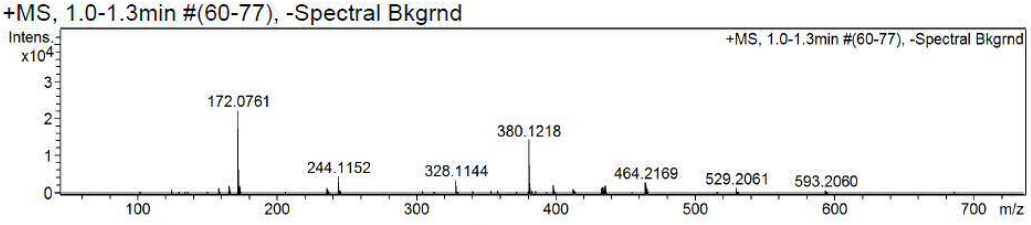

TJN201 HSQC
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

Sample-ID	tn_sel_TJN201	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN201_347748_20_01_52523.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	17/05/2016 14:29:01
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	166.1355	1740	7.9	25	808.6
2	172.0761	22035	100.0	398	11766.6
3	173.0909	1989	9.0	31	1089.7
4	244.1152	4318	19.6	155	3045.3
5	328.1144	3396	15.4	69	1563.0
6	380.1218	14044	63.7	1115	2765.8
7	381.1223	2581	11.7	178	501.9
8	398.1288	1900	8.6	158	353.7
9	433.0283	1635	7.4	119	415.8
10	464.2169	2881	13.1	237	925.2

Crystal structure data for III-41

Table 1. Crystal data and structure refinement for s16sel13.

Identification code	s16sel13	
Empirical formula	C38.50 H44 N6 O10	
Formula weight	750.79	
Temperature	150(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	I2	
Unit cell dimensions	a = 15.7782(8) Å	α= 90°.
	b = 8.2483(5) Å	β= 91.280(5)°.
	c = 28.5263(19) Å	γ = 90°.
Volume	3711.6(4) $Å^3$	
Z	4	
Density (calculated)	1.344 Mg/m^3	
Absorption coefficient	0.816 mm^{-1}	
F(000)	1588	
Crystal size	0.230 x 0.090 x 0.030 mm^3	
Theta range for data collection	3.171 to 66.864°.	
Index ranges	-18<=h<=18, -9<=k<=6, -33<=l<=33	
Reflections collected	9558	
Independent reflections	4650 [R(int) = 0.0551]	
Completeness to theta = 66.864°	99.1 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4650 / 56 / 539	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0732, wR2 = 0.1927	
R indices (all data)	R1 = 0.0859, wR2 = 0.2065	
Absolute structure parameter	0.0(4)	
Extinction coefficient	0.00092(18)	
Largest diff. peak and hole	0.436 and -0.290 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for s16sel13. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	10665(3)	4449(7)	5513(2)	40(1)
N(2)	9983(3)	5610(7)	5578(2)	47(1)
N(3)	9480(3)	3130(7)	5666(2)	40(1)
N(4)	5010(3)	4456(7)	5582(2)	36(1)
N(5)	5705(3)	5584(7)	5552(2)	44(1)
N(6)	4562(3)	6929(7)	5717(2)	44(1)
O(1)	12028(3)	3945(7)	6796(2)	63(2)
O(2)	10725(3)	4164(6)	6467(2)	48(1)
O(3)	10531(4)	7775(7)	6585(2)	68(2)
O(4)	10730(3)	1669(6)	5600(2)	51(1)
O(5)	8592(3)	5363(7)	5795(2)	66(2)
O(6)	5109(3)	2013(8)	6902(2)	69(2)
O(7)	5143(3)	4423(7)	6532(2)	51(1)
O(8)	7005(6)	4340(20)	6519(4)	53(4)
O(8A)	6575(9)	6039(17)	6414(4)	41(3)
O(8B)	7230(7)	3686(17)	6296(5)	31(3)
O(9)	3604(3)	4798(6)	5779(2)	48(1)
O(10)	5836(4)	8308(7)	5698(3)	91(3)
C(1)	11178(5)	3464(10)	6862(3)	55(2)
C(2)	11122(6)	1653(11)	6824(3)	70(2)
C(3)	10828(6)	4117(13)	7309(3)	74(2)
C(4)	12003(4)	5532(11)	6601(3)	56(2)
C(5)	11224(4)	5437(8)	6264(2)	39(1)
C(6)	10642(4)	6959(9)	6249(3)	45(2)
C(7)	10268(4)	7194(8)	5767(3)	45(2)
C(8)	10992(4)	7729(9)	5450(3)	48(2)
C(9)	11741(4)	6514(8)	5516(3)	45(2)
C(10)	11434(4)	5017(8)	5762(2)	39(1)
C(11)	10340(4)	2945(8)	5601(2)	41(2)
C(12)	9274(4)	4761(10)	5701(3)	49(2)
C(13)	8929(4)	1831(9)	5806(3)	44(2)
C(14)	8722(6)	1655(16)	6258(3)	99(4)
C(15)	8206(7)	442(16)	6397(3)	101(4)
C(16)	7864(5)	-644(12)	6073(3)	63(2)

C(17)	8064(5)	-453(9)	5604(3)	54(2)
C(18)	8603(4)	805(9)	5475(3)	45(2)
C(21)	4913(5)	3651(13)	6973(3)	63(2)
C(22)	3990(4)	3870(12)	7038(3)	64(2)
C(23)	5458(5)	4371(17)	7366(3)	83(3)
C(24)	5831(6)	1957(14)	6614(3)	81(3)
C(25)	5694(4)	3390(10)	6284(3)	50(2)
C(26)	6517(4)	4388(14)	6193(3)	69(3)
C(27)	6527(4)	4875(10)	5676(3)	50(2)
C(28)	6647(4)	3370(9)	5386(3)	47(2)
C(29)	5934(4)	2142(9)	5504(2)	43(2)
C(30)	5289(4)	2960(8)	5809(2)	42(2)
C(31)	4305(4)	5321(8)	5713(2)	35(1)
C(32)	5422(4)	7080(9)	5667(3)	52(2)
C(33)	4005(4)	8273(8)	5820(3)	42(2)
C(34)	3868(5)	8622(10)	6283(3)	60(2)
C(35)	3331(6)	9931(12)	6391(3)	72(3)
C(36)	2962(5)	10789(10)	6029(3)	58(2)
C(37)	3100(4)	10422(9)	5580(3)	51(2)
C(38)	3633(4)	9134(9)	5464(3)	48(2)
C(41)	6626(14)	910(30)	7854(10)	146(11)
C(42)	7385(15)	1720(30)	7734(11)	133(10)
C(43)	7431(10)	3430(20)	7601(7)	83(5)
C(44)	8240(12)	4040(30)	7398(8)	110(7)
C(45)	8909(13)	2760(40)	7380(11)	136(10)

Table 3. Bond lengths [Å] for s16sel13.

N(1)-C(11)	1.368(9)
N(1)-N(2)	1.455(7)
N(1)-C(10)	1.469(8)
N(2)-C(12)	1.373(9)
N(2)-C(7)	1.479(9)
N(3)-C(11)	1.381(8)
N(3)-C(12)	1.388(10)
N(3)-C(13)	1.441(8)
N(4)-C(31)	1.380(8)
N(4)-N(5)	1.442(7)
N(4)-C(30)	1.457(8)
N(5)-C(32)	1.355(9)
N(5)-C(27)	1.458(9)
N(6)-C(32)	1.372(8)
N(6)-C(31)	1.387(9)
N(6)-C(33)	1.450(8)
O(1)-C(1)	1.415(9)
O(1)-C(4)	1.424(10)
O(2)-C(5)	1.441(8)
O(2)-C(1)	1.443(9)
O(3)-C(6)	1.189(8)
O(4)-C(11)	1.219(8)
O(5)-C(12)	1.220(8)
O(6)-C(21)	1.401(11)
O(6)-C(24)	1.420(9)
O(7)-C(25)	1.419(8)
O(7)-C(21)	1.462(9)
O(8)-C(26)	1.195(12)
O(8A)-C(26)	1.503(16)
O(8B)-C(26)	1.293(15)
O(9)-C(31)	1.207(7)
O(10)-C(32)	1.208(9)
C(1)-C(2)	1.500(12)
C(1)-C(3)	1.501(10)
C(2)-H(2A)	0.9800
C(2)-H(2B)	0.9800
C(2)-H(2C)	0.9800

C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-C(5)	1.545(9)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(10)	1.518(9)
C(5)-C(6)	1.555(9)
C(6)-C(7)	1.497(10)
C(7)-C(8)	1.538(10)
C(7)-H(7)	1.0000
C(8)-C(9)	1.558(9)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.505(9)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-H(10)	1.0000
C(13)-C(14)	1.346(11)
C(13)-C(18)	1.360(10)
C(14)-C(15)	1.355(14)
C(14)-H(14)	0.9500
C(15)-C(16)	1.388(13)
C(15)-H(15)	0.9500
C(16)-C(17)	1.391(11)
C(16)-H(16)	0.9500
C(17)-C(18)	1.396(10)
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500
C(21)-C(22)	1.484(10)
C(21)-C(23)	1.518(12)
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-C(25)	1.525(12)
C(24)-H(24A)	0.9900

C(24)-H(24B)	0.9900
C(25)-C(30)	1.525(10)
C(25)-C(26)	1.563(11)
C(26)-C(27)	1.528(11)
C(27)-C(28)	1.506(10)
C(27)-H(27)	1.0000
C(28)-C(29)	1.557(10)
C(28)-H(28A)	0.9900
C(28)-H(28B)	0.9900
C(29)-C(30)	1.514(9)
C(29)-H(29A)	0.9900
C(29)-H(29B)	0.9900
C(30)-H(30)	1.0000
C(33)-C(38)	1.361(10)
C(33)-C(34)	1.374(10)
C(34)-C(35)	1.410(11)
C(34)-H(34)	0.9500
C(35)-C(36)	1.371(11)
C(35)-H(35)	0.9500
C(36)-C(37)	1.337(11)
C(36)-H(36)	0.9500
C(37)-C(38)	1.399(10)
C(37)-H(37)	0.9500
C(38)-H(38)	0.9500
C(41)-C(42)	1.422(18)
C(41)-H(41A)	0.9800
C(41)-H(41B)	0.9800
C(41)-H(41C)	0.9800
C(42)-C(43)	1.458(18)
C(42)-H(42A)	0.9900
C(42)-H(42B)	0.9900
C(43)-C(44)	1.500(16)
C(43)-H(43A)	0.9900
C(43)-H(43B)	0.9900
C(44)-C(45)	1.49(2)
C(44)-H(44A)	0.9900
C(44)-H(44B)	0.9900
C(45)-H(45A)	0.9800
C(45)-H(45B)	0.9800

C(45)-H(45C)	0.9800

Table 4. Bond angles [°] for s16sel13.

C(11)-N(1)-N(2)	106.9(5)
C(11)-N(1)-C(10)	120.6(6)
N(2)-N(1)-C(10)	109.5(5)
C(12)-N(2)-N(1)	107.8(6)
C(12)-N(2)-C(7)	126.8(6)
N(1)-N(2)-C(7)	114.1(5)
C(11)-N(3)-C(12)	110.4(5)
C(11)-N(3)-C(13)	123.7(6)
C(12)-N(3)-C(13)	123.8(5)
C(31)-N(4)-N(5)	107.5(5)
C(31)-N(4)-C(30)	123.7(5)
N(5)-N(4)-C(30)	110.5(5)
C(32)-N(5)-N(4)	108.6(5)
C(32)-N(5)-C(27)	127.1(6)
N(4)-N(5)-C(27)	113.6(6)
C(32)-N(6)-C(31)	112.0(6)
C(32)-N(6)-C(33)	123.9(6)
C(31)-N(6)-C(33)	123.7(5)
C(1)-O(1)-C(4)	107.0(6)
C(5)-O(2)-C(1)	109.9(5)
C(21)-O(6)-C(24)	107.3(7)
C(25)-O(7)-C(21)	109.6(6)
O(1)-C(1)-O(2)	103.8(5)
O(1)-C(1)-C(2)	108.9(7)
O(2)-C(1)-C(2)	108.3(7)
O(1)-C(1)-C(3)	112.3(7)
O(2)-C(1)-C(3)	109.6(7)
C(2)-C(1)-C(3)	113.4(7)
C(1)-C(2)-H(2A)	109.5
C(1)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5
C(1)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
C(1)-C(3)-H(3A)	109.5
C(1)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5

C(1)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
O(1)-C(4)-C(5)	102.3(6)
O(1)-C(4)-H(4A)	111.3
C(5)-C(4)-H(4A)	111.3
O(1)-C(4)-H(4B)	111.3
C(5)-C(4)-H(4B)	111.3
H(4A)-C(4)-H(4B)	109.2
O(2)-C(5)-C(10)	110.2(5)
O(2)-C(5)-C(4)	102.8(5)
C(10)-C(5)-C(4)	114.3(5)
O(2)-C(5)-C(6)	105.8(5)
C(10)-C(5)-C(6)	107.5(5)
C(4)-C(5)-C(6)	115.9(6)
O(3)-C(6)-C(7)	127.3(7)
O(3)-C(6)-C(5)	122.2(7)
C(7)-C(6)-C(5)	110.5(6)
N(2)-C(7)-C(6)	109.3(6)
N(2)-C(7)-C(8)	105.2(6)
C(6)-C(7)-C(8)	107.1(5)
N(2)-C(7)-H(7)	111.6
C(6)-C(7)-H(7)	111.6
C(8)-C(7)-H(7)	111.6
C(7)-C(8)-C(9)	108.4(6)
C(7)-C(8)-H(8A)	110.0
C(9)-C(8)-H(8A)	110.0
C(7)-C(8)-H(8B)	110.0
C(9)-C(8)-H(8B)	110.0
H(8A)-C(8)-H(8B)	108.4
C(10)-C(9)-C(8)	109.5(5)
C(10)-C(9)-H(9A)	109.8
C(8)-C(9)-H(9A)	109.8
C(10)-C(9)-H(9B)	109.8
C(8)-C(9)-H(9B)	109.8
H(9A)-C(9)-H(9B)	108.2
N(1)-C(10)-C(9)	107.9(6)
N(1)-C(10)-C(5)	109.5(5)
C(9)-C(10)-C(5)	109.3(5)

N(1)-C(10)-H(10)	110.0
C(9)-C(10)-H(10)	110.0
C(5)-C(10)-H(10)	110.0
O(4)-C(11)-N(1)	126.2(6)
O(4)-C(11)-N(3)	126.3(6)
N(1)-C(11)-N(3)	107.4(5)
O(5)-C(12)-N(2)	125.2(7)
O(5)-C(12)-N(3)	128.3(7)
N(2)-C(12)-N(3)	106.4(6)
C(14)-C(13)-C(18)	120.1(7)
C(14)-C(13)-N(3)	120.4(7)
C(18)-C(13)-N(3)	119.4(6)
C(13)-C(14)-C(15)	121.4(9)
C(13)-C(14)-H(14)	119.3
C(15)-C(14)-H(14)	119.3
C(14)-C(15)-C(16)	120.6(9)
C(14)-C(15)-H(15)	119.7
C(16)-C(15)-H(15)	119.7
C(15)-C(16)-C(17)	118.4(8)
C(15)-C(16)-H(16)	120.8
C(17)-C(16)-H(16)	120.8
C(16)-C(17)-C(18)	119.3(7)
C(16)-C(17)-H(17)	120.3
C(18)-C(17)-H(17)	120.3
C(13)-C(18)-C(17)	120.2(7)
C(13)-C(18)-H(18)	119.9
C(17)-C(18)-H(18)	119.9
O(6)-C(21)-O(7)	103.7(6)
O(6)-C(21)-C(22)	110.8(7)
O(7)-C(21)-C(22)	108.5(6)
O(6)-C(21)-C(23)	111.2(8)
O(7)-C(21)-C(23)	108.5(7)
C(22)-C(21)-C(23)	113.6(7)
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5

C(21)-C(23)-H(23A)	109.5
C(21)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(21)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
O(6)-C(24)-C(25)	103.2(6)
O(6)-C(24)-H(24A)	111.1
C(25)-C(24)-H(24A)	111.1
O(6)-C(24)-H(24B)	111.1
C(25)-C(24)-H(24B)	111.1
H(24A)-C(24)-H(24B)	109.1
O(7)-C(25)-C(24)	103.7(6)
O(7)-C(25)-C(30)	109.5(5)
C(24)-C(25)-C(30)	114.8(8)
O(7)-C(25)-C(26)	106.7(6)
C(24)-C(25)-C(26)	113.8(7)
C(30)-C(25)-C(26)	108.0(6)
O(8)-C(26)-C(27)	137.6(9)
O(8B)-C(26)-C(27)	108.1(9)
O(8A)-C(26)-C(27)	99.4(9)
O(8)-C(26)-C(25)	112.1(10)
O(8B)-C(26)-C(25)	116.6(10)
O(8A)-C(26)-C(25)	116.8(7)
C(27)-C(26)-C(25)	109.0(6)
N(5)-C(27)-C(28)	108.7(6)
N(5)-C(27)-C(26)	108.1(5)
C(28)-C(27)-C(26)	108.5(7)
N(5)-C(27)-H(27)	110.5
C(28)-C(27)-H(27)	110.5
C(26)-C(27)-H(27)	110.5
C(27)-C(28)-C(29)	108.5(5)
C(27)-C(28)-H(28A)	110.0
C(29)-C(28)-H(28A)	110.0
C(27)-C(28)-H(28B)	110.0
C(29)-C(28)-H(28B)	110.0
H(28A)-C(28)-H(28B)	108.4
C(30)-C(29)-C(28)	109.4(6)
C(30)-C(29)-H(29A)	109.8

C(28)-C(29)-H(29A)	109.8
C(30)-C(29)-H(29B)	109.8
C(28)-C(29)-H(29B)	109.8
H(29A)-C(29)-H(29B)	108.2
N(4)-C(30)-C(29)	108.7(5)
N(4)-C(30)-C(25)	108.3(6)
C(29)-C(30)-C(25)	109.9(5)
N(4)-C(30)-H(30)	110.0
C(29)-C(30)-H(30)	110.0
C(25)-C(30)-H(30)	110.0
O(9)-C(31)-N(4)	127.3(6)
O(9)-C(31)-N(6)	127.5(6)
N(4)-C(31)-N(6)	105.0(5)
O(10)-C(32)-N(5)	126.9(6)
O(10)-C(32)-N(6)	127.0(7)
N(5)-C(32)-N(6)	105.9(6)
C(38)-C(33)-C(34)	122.3(6)
C(38)-C(33)-N(6)	120.0(6)
C(34)-C(33)-N(6)	117.7(6)
C(33)-C(34)-C(35)	118.5(7)
C(33)-C(34)-H(34)	120.8
C(35)-C(34)-H(34)	120.8
C(36)-C(35)-C(34)	118.6(8)
C(36)-C(35)-H(35)	120.7
C(34)-C(35)-H(35)	120.7
C(37)-C(36)-C(35)	121.9(8)
C(37)-C(36)-H(36)	119.1
C(35)-C(36)-H(36)	119.1
C(36)-C(37)-C(38)	120.7(7)
C(36)-C(37)-H(37)	119.7
C(38)-C(37)-H(37)	119.7
C(33)-C(38)-C(37)	118.1(7)
C(33)-C(38)-H(38)	121.0
C(37)-C(38)-H(38)	121.0
C(42)-C(41)-H(41A)	109.5
C(42)-C(41)-H(41B)	109.5
H(41A)-C(41)-H(41B)	109.5
C(42)-C(41)-H(41C)	109.5
H(41A)-C(41)-H(41C)	109.5

H(41B)-C(41)-H(41C)	109.5
C(41)-C(42)-C(43)	124.3(19)
C(41)-C(42)-H(42A)	106.3
C(43)-C(42)-H(42A)	106.3
C(41)-C(42)-H(42B)	106.3
C(43)-C(42)-H(42B)	106.3
H(42A)-C(42)-H(42B)	106.4
C(42)-C(43)-C(44)	118.2(14)
C(42)-C(43)-H(43A)	107.8
C(44)-C(43)-H(43A)	107.8
C(42)-C(43)-H(43B)	107.8
C(44)-C(43)-H(43B)	107.8
H(43A)-C(43)-H(43B)	107.1
C(45)-C(44)-C(43)	112.6(13)
C(45)-C(44)-H(44A)	109.1
C(43)-C(44)-H(44A)	109.1
C(45)-C(44)-H(44B)	109.1
C(43)-C(44)-H(44B)	109.1
H(44A)-C(44)-H(44B)	107.8
C(44)-C(45)-H(45A)	109.5
C(44)-C(45)-H(45B)	109.5
H(45A)-C(45)-H(45B)	109.5
C(44)-C(45)-H(45C)	109.5
H(45A)-C(45)-H(45C)	109.5
H(45B)-C(45)-H(45C)	109.5

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for s16sel13. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	29(2)	32(3)	60(3)	-6(3)	10(2)	8(2)
N(2)	35(3)	38(3)	67(4)	-8(3)	5(3)	-2(2)
N(3)	38(3)	30(3)	54(3)	-6(2)	5(2)	-5(2)
N(4)	30(2)	32(3)	46(3)	-3(2)	4(2)	-2(2)
N(5)	37(3)	35(3)	61(4)	-3(3)	14(2)	-4(2)
N(6)	39(3)	36(3)	59(3)	6(3)	16(2)	6(3)
O(1)	44(3)	72(4)	72(3)	21(3)	-1(2)	-5(3)
O(2)	42(2)	47(3)	57(3)	2(2)	10(2)	-4(2)
O(3)	86(4)	49(3)	71(4)	-21(3)	12(3)	4(3)
O(4)	56(3)	32(3)	66(3)	-8(2)	17(2)	0(2)
O(5)	31(2)	52(4)	115(5)	-17(3)	12(3)	3(2)
O(6)	65(3)	75(4)	68(4)	23(3)	12(3)	16(3)
O(7)	41(2)	66(3)	45(3)	4(2)	8(2)	9(2)
O(8)	19(5)	119(12)	23(5)	-21(7)	-5(4)	-5(6)
O(8A)	64(9)	34(7)	25(6)	-20(5)	12(6)	-24(7)
O(8B)	15(6)	32(7)	45(8)	16(6)	-11(5)	-1(5)
O(9)	36(2)	45(3)	62(3)	-2(2)	3(2)	3(2)
O(10)	58(3)	39(3)	178(8)	-22(4)	51(4)	-15(3)
C(1)	55(4)	60(5)	52(4)	9(3)	8(3)	-2(4)
C(2)	76(5)	61(5)	73(6)	14(4)	24(4)	-4(4)
C(3)	85(6)	88(7)	49(4)	1(5)	19(4)	-13(5)
C(4)	49(4)	66(5)	55(4)	11(4)	-4(3)	-11(4)
C(5)	28(3)	43(4)	47(3)	0(3)	3(2)	-4(3)
C(6)	38(3)	36(4)	60(4)	-6(3)	11(3)	-7(3)
C(7)	39(3)	26(3)	70(5)	-6(3)	7(3)	2(3)
C(8)	42(3)	34(4)	66(5)	3(3)	-1(3)	5(3)
C(9)	31(3)	37(4)	67(4)	4(3)	8(3)	1(3)
C(10)	30(3)	27(3)	60(4)	-1(3)	7(3)	1(2)
C(11)	44(3)	28(3)	51(4)	-10(3)	10(3)	1(3)
C(12)	30(3)	52(5)	64(5)	-5(4)	2(3)	-9(3)
C(13)	32(3)	46(4)	55(4)	-7(3)	9(3)	-9(3)
C(14)	88(6)	146(11)	64(6)	-36(6)	32(5)	-72(7)
C(15)	114(8)	130(11)	60(5)	-26(6)	31(5)	-69(8)
C(16)	50(4)	70(6)	69(5)	-8(4)	13(3)	-19(4)

C(17)	65(5)	35(4)	62(5)	-3(3)	2(4)	-4(3)
C(18)	52(4)	33(4)	50(4)	-10(3)	1(3)	-1(3)
C(21)	50(4)	95(7)	45(4)	10(4)	5(3)	10(4)
C(22)	50(4)	69(5)	75(5)	6(4)	17(4)	-4(4)
C(23)	60(5)	141(10)	49(4)	-3(6)	-2(4)	4(6)
C(24)	83(6)	105(8)	55(5)	24(5)	17(4)	41(6)
C(25)	40(3)	62(5)	49(4)	4(4)	8(3)	12(3)
C(26)	36(4)	111(8)	63(5)	-27(5)	12(3)	8(4)
C(27)	39(3)	48(4)	62(4)	-8(3)	15(3)	-3(3)
C(28)	41(3)	51(4)	50(4)	-6(3)	12(3)	4(3)
C(29)	46(4)	32(4)	52(4)	-3(3)	3(3)	4(3)
C(30)	40(3)	30(3)	55(4)	4(3)	4(3)	2(3)
C(31)	29(3)	35(4)	42(3)	-2(3)	3(2)	3(3)
C(32)	52(4)	28(4)	77(5)	-10(4)	21(4)	-5(3)
C(33)	37(3)	23(3)	65(4)	3(3)	12(3)	2(3)
C(34)	86(5)	47(5)	47(4)	2(3)	8(4)	21(4)
C(35)	90(6)	64(6)	63(5)	1(4)	15(4)	31(5)
C(36)	62(5)	40(4)	71(5)	4(4)	22(4)	10(4)
C(37)	41(3)	38(4)	74(5)	16(4)	10(3)	4(3)
C(38)	41(3)	48(4)	53(4)	5(3)	7(3)	8(3)
C(41)	112(15)	180(20)	146(18)	87(16)	-76(14)	-16(15)
C(42)	125(13)	136(14)	137(13)	35(11)	9(10)	25(11)
C(43)	80(9)	97(11)	72(9)	-9(8)	6(8)	3(8)
C(44)	98(11)	139(13)	92(11)	-14(10)	-12(9)	-7(10)
C(45)	142(18)	111(17)	154(19)	15(16)	25(16)	-13(15)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for s16sel13.

	x	y	z	U(eq)
H(2A)	10532	1311	6859	104
H(2B)	11476	1154	7071	104
H(2C)	11321	1310	6516	104
H(3A)	10239	3765	7338	111
H(3B)	10852	5304	7305	111
H(3C)	11166	3708	7577	111
H(4A)	12526	5775	6429	68
H(4B)	11924	6364	6846	68
H(7)	9796	8004	5765	54
H(8A)	11180	8838	5536	57
H(8B)	10795	7739	5118	57
H(9A)	11967	6218	5206	54
H(9B)	12203	7026	5704	54
H(10)	11880	4156	5757	47
H(14)	8942	2397	6485	119
H(15)	8077	333	6720	121
H(16)	7502	-1496	6169	75
H(17)	7836	-1172	5373	65
H(18)	8743	944	5156	54
H(22A)	3853	5029	7035	96
H(22B)	3831	3403	7340	96
H(22C)	3675	3323	6784	96
H(23A)	5343	5536	7390	125
H(23B)	6058	4202	7299	125
H(23C)	5323	3840	7663	125
H(24A)	5854	923	6439	97
H(24B)	6361	2084	6803	97
H(27)	6992	5670	5620	59
H(28A)	7209	2887	5458	57
H(28B)	6619	3646	5048	57
H(29A)	5654	1754	5210	52
H(29B)	6181	1194	5670	52
H(30)	4793	2225	5854	50

H(34)	4129	7996	6526	72
H(35)	3228	10213	6707	86
H(36)	2597	11669	6098	69
H(37)	2833	11042	5338	61
H(38)	3732	8869	5146	57
H(41A)	6291	677	7568	219
H(41B)	6296	1604	8061	219
H(41C)	6766	-106	8016	219
H(42A)	7627	1101	7472	159
H(42B)	7782	1585	8005	159
H(43A)	7313	4083	7882	99
H(43B)	6968	3639	7369	99
H(44A)	8122	4449	7077	132
H(44B)	8454	4956	7591	132
H(45A)	9435	3237	7267	203
H(45B)	8722	1895	7166	203
H(45C)	9008	2309	7694	203

Table 7. Torsion angles [°] for s16sel13.

C(11)-N(1)-N(2)-C(12)	-0.2(7)
C(10)-N(1)-N(2)-C(12)	-132.4(6)
C(11)-N(1)-N(2)-C(7)	146.2(6)
C(10)-N(1)-N(2)-C(7)	14.0(8)
C(31)-N(4)-N(5)-C(32)	0.5(7)
C(30)-N(4)-N(5)-C(32)	-137.1(6)
C(31)-N(4)-N(5)-C(27)	147.8(5)
C(30)-N(4)-N(5)-C(27)	10.2(7)
C(4)-O(1)-C(1)-O(2)	35.8(8)
C(4)-O(1)-C(1)-C(2)	151.0(7)
C(4)-O(1)-C(1)-C(3)	-82.5(8)
C(5)-O(2)-C(1)-O(1)	-18.5(8)
C(5)-O(2)-C(1)-C(2)	-134.1(6)
C(5)-O(2)-C(1)-C(3)	101.7(7)
C(1)-O(1)-C(4)-C(5)	-38.0(7)
C(1)-O(2)-C(5)-C(10)	118.0(6)
C(1)-O(2)-C(5)-C(4)	-4.2(7)
C(1)-O(2)-C(5)-C(6)	-126.1(6)
O(1)-C(4)-C(5)-O(2)	25.0(7)
O(1)-C(4)-C(5)-C(10)	-94.4(7)
O(1)-C(4)-C(5)-C(6)	139.8(6)
O(2)-C(5)-C(6)-O(3)	79.5(8)
C(10)-C(5)-C(6)-O(3)	-162.8(6)
C(4)-C(5)-C(6)-O(3)	-33.6(9)
O(2)-C(5)-C(6)-C(7)	-100.2(6)
C(10)-C(5)-C(6)-C(7)	17.5(7)
C(4)-C(5)-C(6)-C(7)	146.7(6)
C(12)-N(2)-C(7)-C(6)	75.2(8)
N(1)-N(2)-C(7)-C(6)	-63.8(7)
C(12)-N(2)-C(7)-C(8)	-170.1(7)
N(1)-N(2)-C(7)-C(8)	51.0(7)
O(3)-C(6)-C(7)-N(2)	-136.5(7)
C(5)-C(6)-C(7)-N(2)	43.2(7)
O(3)-C(6)-C(7)-C(8)	109.9(8)
C(5)-C(6)-C(7)-C(8)	-70.4(7)
N(2)-C(7)-C(8)-C(9)	-65.2(7)
C(6)-C(7)-C(8)-C(9)	51.1(7)

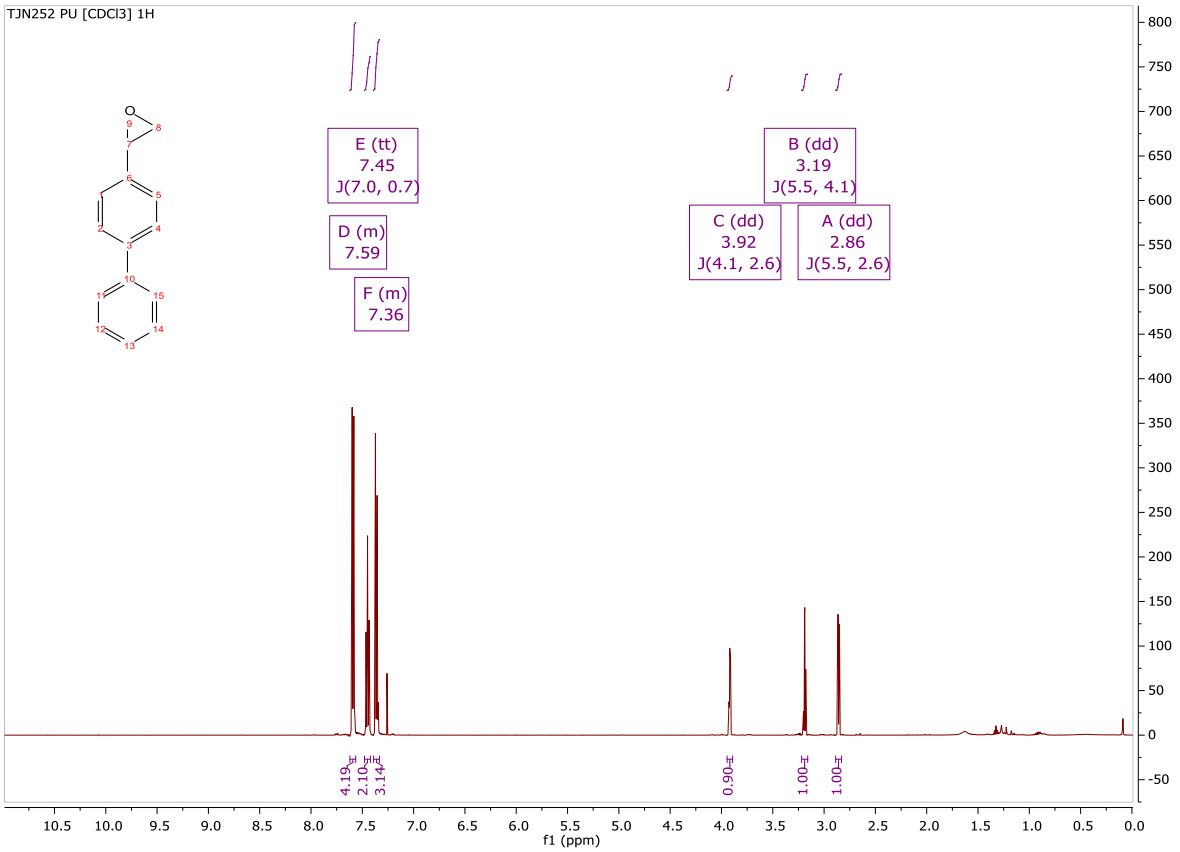
C(7)-C(8)-C(9)-C(10)	14.6(8)
C(11)-N(1)-C(10)-C(9)	167.4(5)
N(2)-N(1)-C(10)-C(9)	-68.0(6)
C(11)-N(1)-C(10)-C(5)	-73.6(7)
N(2)-N(1)-C(10)-C(5)	51.0(7)
C(8)-C(9)-C(10)-N(1)	50.4(7)
C(8)-C(9)-C(10)-C(5)	-68.6(7)
O(2)-C(5)-C(10)-N(1)	46.8(7)
C(4)-C(5)-C(10)-N(1)	161.9(6)
C(6)-C(5)-C(10)-N(1)	-68.0(6)
O(2)-C(5)-C(10)-C(9)	164.8(5)
C(4)-C(5)-C(10)-C(9)	-80.1(7)
C(6)-C(5)-C(10)-C(9)	50.0(6)
N(2)-N(1)-C(11)-O(4)	-177.0(7)
C(10)-N(1)-C(11)-O(4)	-51.2(10)
N(2)-N(1)-C(11)-N(3)	6.4(7)
C(10)-N(1)-C(11)-N(3)	132.2(6)
C(12)-N(3)-C(11)-O(4)	172.9(7)
C(13)-N(3)-C(11)-O(4)	8.8(11)
C(12)-N(3)-C(11)-N(1)	-10.5(8)
C(13)-N(3)-C(11)-N(1)	-174.6(6)
N(1)-N(2)-C(12)-O(5)	177.9(7)
C(7)-N(2)-C(12)-O(5)	37.0(12)
N(1)-N(2)-C(12)-N(3)	-5.9(8)
C(7)-N(2)-C(12)-N(3)	-146.9(7)
C(11)-N(3)-C(12)-O(5)	-173.8(8)
C(13)-N(3)-C(12)-O(5)	-9.7(13)
C(11)-N(3)-C(12)-N(2)	10.2(8)
C(13)-N(3)-C(12)-N(2)	174.4(6)
C(11)-N(3)-C(13)-C(14)	97.6(10)
C(12)-N(3)-C(13)-C(14)	-64.5(11)
C(11)-N(3)-C(13)-C(18)	-83.9(9)
C(12)-N(3)-C(13)-C(18)	114.0(8)
C(18)-C(13)-C(14)-C(15)	1.6(18)
N(3)-C(13)-C(14)-C(15)	-179.9(11)
C(13)-C(14)-C(15)-C(16)	-1(2)
C(14)-C(15)-C(16)-C(17)	0.0(18)
C(15)-C(16)-C(17)-C(18)	0.5(14)
C(14)-C(13)-C(18)-C(17)	-1.1(13)

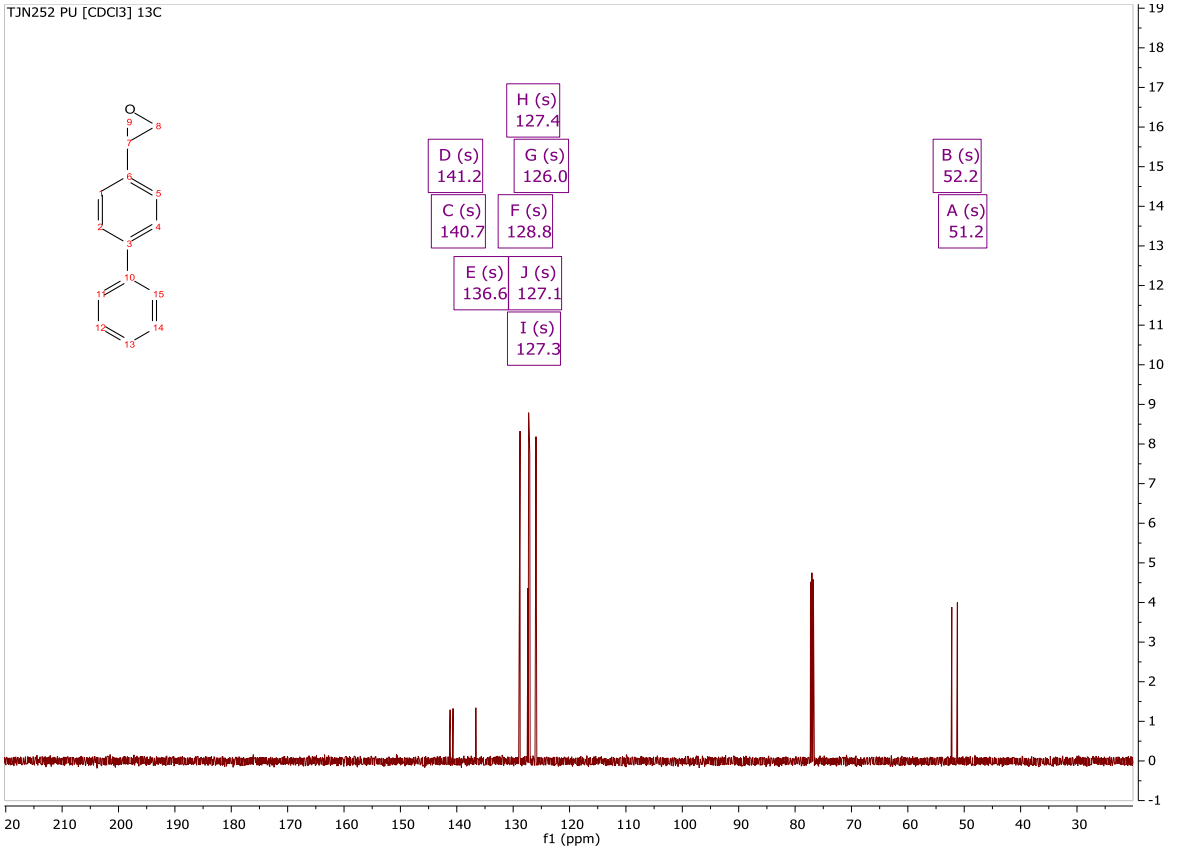
N(3)-C(13)-C(18)-C(17)	-179.6(6)
C(16)-C(17)-C(18)-C(13)	0.0(12)
C(24)-O(6)-C(21)-O(7)	33.8(8)
C(24)-O(6)-C(21)-C(22)	150.1(7)
C(24)-O(6)-C(21)-C(23)	-82.5(8)
C(25)-O(7)-C(21)-O(6)	-18.2(7)
C(25)-O(7)-C(21)-C(22)	-136.1(7)
C(25)-O(7)-C(21)-C(23)	100.0(8)
C(21)-O(6)-C(24)-C(25)	-35.8(9)
C(21)-O(7)-C(25)-C(24)	-3.1(8)
C(21)-O(7)-C(25)-C(30)	119.9(6)
C(21)-O(7)-C(25)-C(26)	-123.5(7)
O(6)-C(24)-C(25)-O(7)	22.9(9)
O(6)-C(24)-C(25)-C(30)	-96.4(8)
O(6)-C(24)-C(25)-C(26)	138.4(8)
O(7)-C(25)-C(26)-O(8)	84.6(12)
C(24)-C(25)-C(26)-O(8)	-29.1(13)
C(30)-C(25)-C(26)-O(8)	-157.8(11)
O(7)-C(25)-C(26)-O(8B)	131.3(11)
C(24)-C(25)-C(26)-O(8B)	17.6(13)
C(30)-C(25)-C(26)-O(8B)	-111.1(11)
O(7)-C(25)-C(26)-O(8A)	5.5(11)
C(24)-C(25)-C(26)-O(8A)	-108.2(11)
C(30)-C(25)-C(26)-O(8A)	123.1(9)
O(7)-C(25)-C(26)-C(27)	-106.1(7)
C(24)-C(25)-C(26)-C(27)	140.2(8)
C(30)-C(25)-C(26)-C(27)	11.5(9)
C(32)-N(5)-C(27)-C(28)	-167.0(6)
N(4)-N(5)-C(27)-C(28)	53.0(7)
C(32)-N(5)-C(27)-C(26)	75.5(9)
N(4)-N(5)-C(27)-C(26)	-64.5(8)
O(8)-C(26)-C(27)-N(5)	-145.4(17)
O(8B)-C(26)-C(27)-N(5)	176.9(9)
O(8A)-C(26)-C(27)-N(5)	-73.4(9)
C(25)-C(26)-C(27)-N(5)	49.3(9)
O(8)-C(26)-C(27)-C(28)	97.0(19)
O(8B)-C(26)-C(27)-C(28)	59.2(11)
O(8A)-C(26)-C(27)-C(28)	168.9(8)
C(25)-C(26)-C(27)-C(28)	-68.4(8)

N(5)-C(27)-C(28)-C(29)	-61.3(8)
C(26)-C(27)-C(28)-C(29)	56.0(7)
C(27)-C(28)-C(29)-C(30)	8.6(8)
C(31)-N(4)-C(30)-C(29)	165.9(6)
N(5)-N(4)-C(30)-C(29)	-64.6(7)
C(31)-N(4)-C(30)-C(25)	-74.7(7)
N(5)-N(4)-C(30)-C(25)	54.8(6)
C(28)-C(29)-C(30)-N(4)	52.7(7)
C(28)-C(29)-C(30)-C(25)	-65.7(7)
O(7)-C(25)-C(30)-N(4)	50.2(7)
C(24)-C(25)-C(30)-N(4)	166.3(6)
C(26)-C(25)-C(30)-N(4)	-65.5(7)
O(7)-C(25)-C(30)-C(29)	168.9(6)
C(24)-C(25)-C(30)-C(29)	-75.1(7)
C(26)-C(25)-C(30)-C(29)	53.1(8)
N(5)-N(4)-C(31)-O(9)	-179.0(6)
C(30)-N(4)-C(31)-O(9)	-48.3(10)
N(5)-N(4)-C(31)-N(6)	5.2(7)
C(30)-N(4)-C(31)-N(6)	135.9(6)
C(32)-N(6)-C(31)-O(9)	174.8(7)
C(33)-N(6)-C(31)-O(9)	1.9(11)
C(32)-N(6)-C(31)-N(4)	-9.4(8)
C(33)-N(6)-C(31)-N(4)	177.8(6)
N(4)-N(5)-C(32)-O(10)	176.7(9)
C(27)-N(5)-C(32)-O(10)	35.1(14)
N(4)-N(5)-C(32)-N(6)	-6.1(8)
C(27)-N(5)-C(32)-N(6)	-147.7(7)
C(31)-N(6)-C(32)-O(10)	-173.0(9)
C(33)-N(6)-C(32)-O(10)	-0.2(14)
C(31)-N(6)-C(32)-N(5)	9.8(9)
C(33)-N(6)-C(32)-N(5)	-177.4(6)
C(32)-N(6)-C(33)-C(38)	90.5(9)
C(31)-N(6)-C(33)-C(38)	-97.5(8)
C(32)-N(6)-C(33)-C(34)	-89.9(9)
C(31)-N(6)-C(33)-C(34)	82.1(9)
C(38)-C(33)-C(34)-C(35)	-0.8(12)
N(6)-C(33)-C(34)-C(35)	179.7(7)
C(33)-C(34)-C(35)-C(36)	0.7(14)
C(34)-C(35)-C(36)-C(37)	-0.3(14)

C(35)-C(36)-C(37)-C(38)	0.0(13)
C(34)-C(33)-C(38)-C(37)	0.5(11)
N(6)-C(33)-C(38)-C(37)	-180.0(6)
C(36)-C(37)-C(38)-C(33)	0.0(11)
C(41)-C(42)-C(43)-C(44)	-169(3)
C(42)-C(43)-C(44)-C(45)	-2(3)

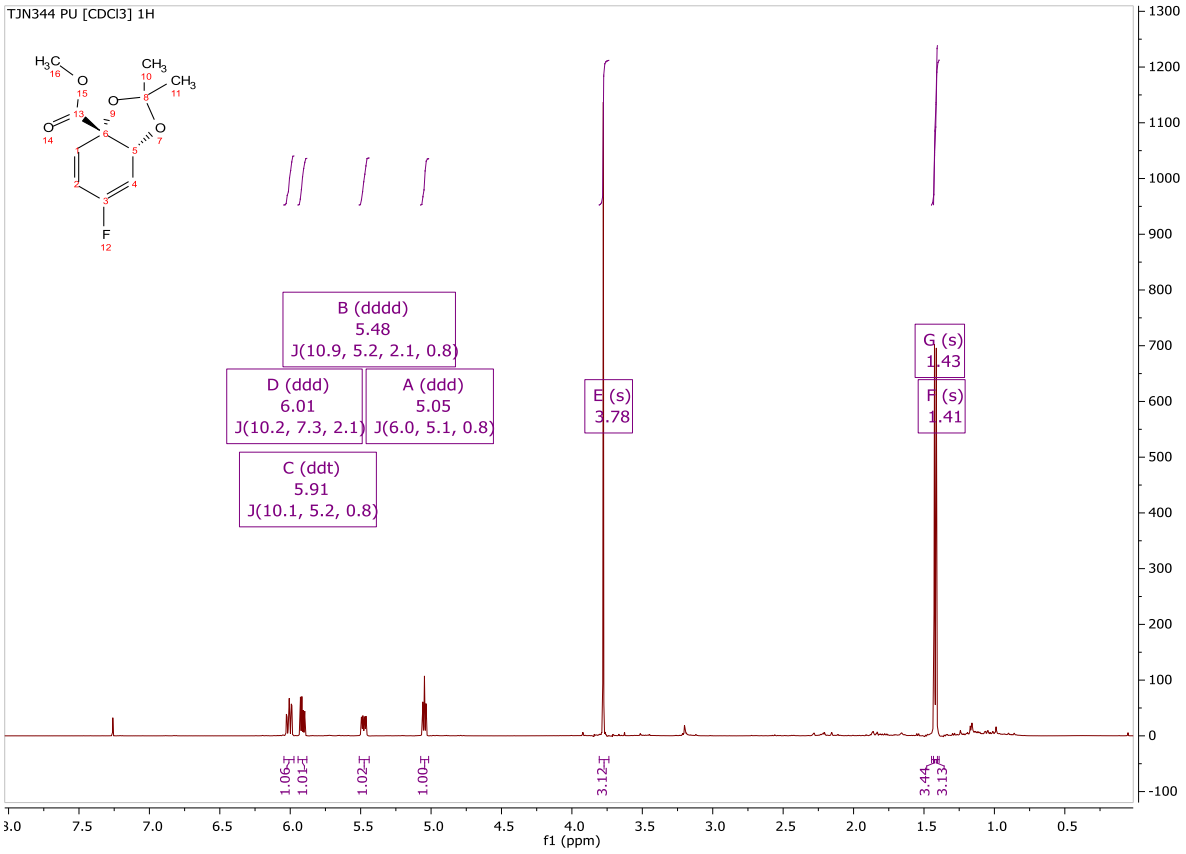
2-([1,1'-biphenyl]-4-yl)oxirane III-62

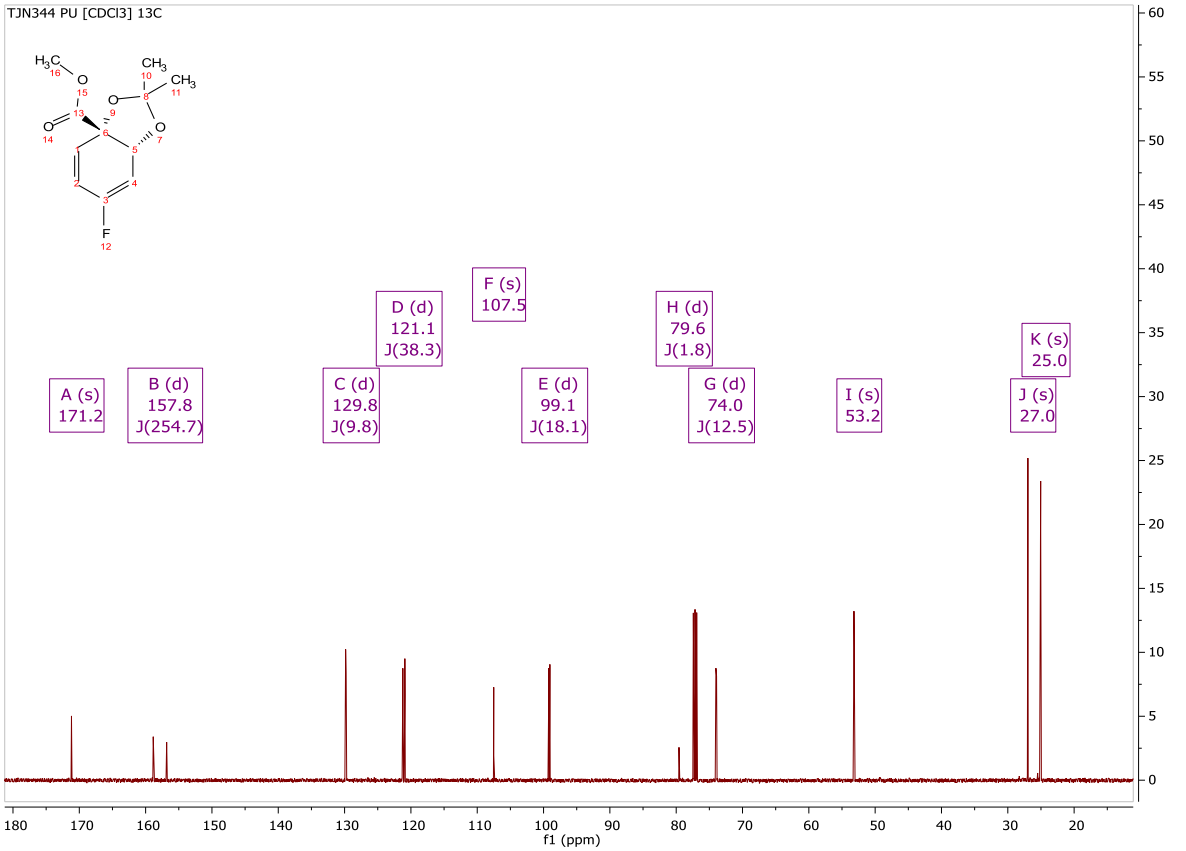


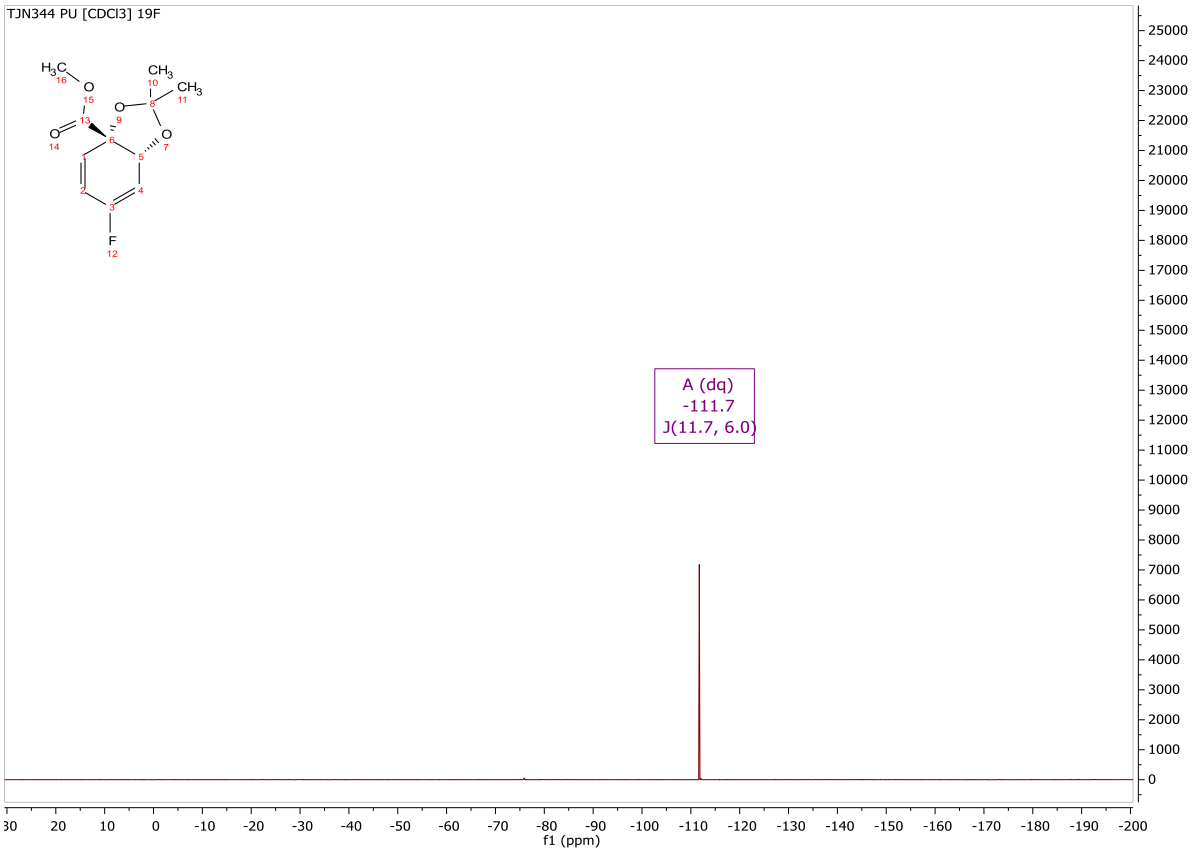


Exploiting a fluoro-arene *ipso,ortho*-diol in synthesis: data

Methyl (3a*S*,7a*R*)-6-fluoro-2,2-dimethylbenzo[d][1,3]dioxole-3a(7aH)-carboxylate IV-30



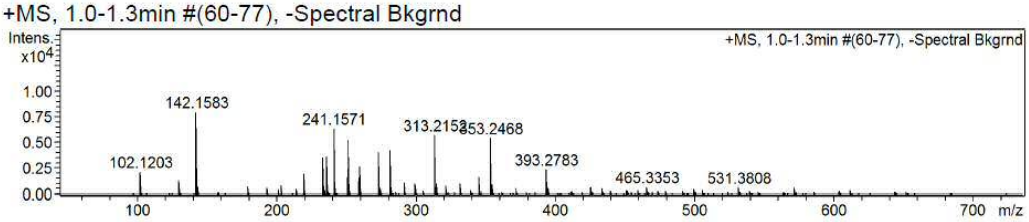




Confirmation of Expected Formula

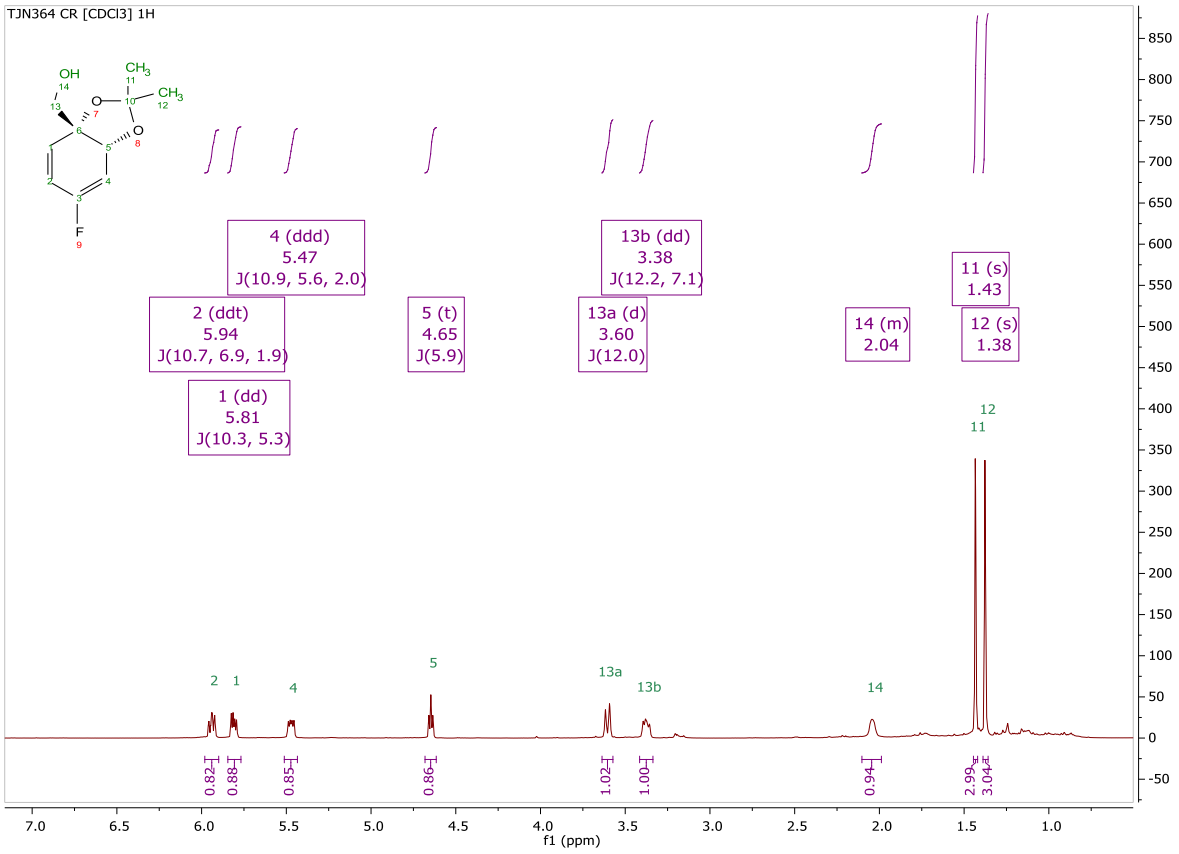
Sample-ID	tn_sel_TJN344	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN344_351491_64_01_56892.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	27/03/2017 14:33:24
Ionisation Mode	positive electrospray (ESI)		

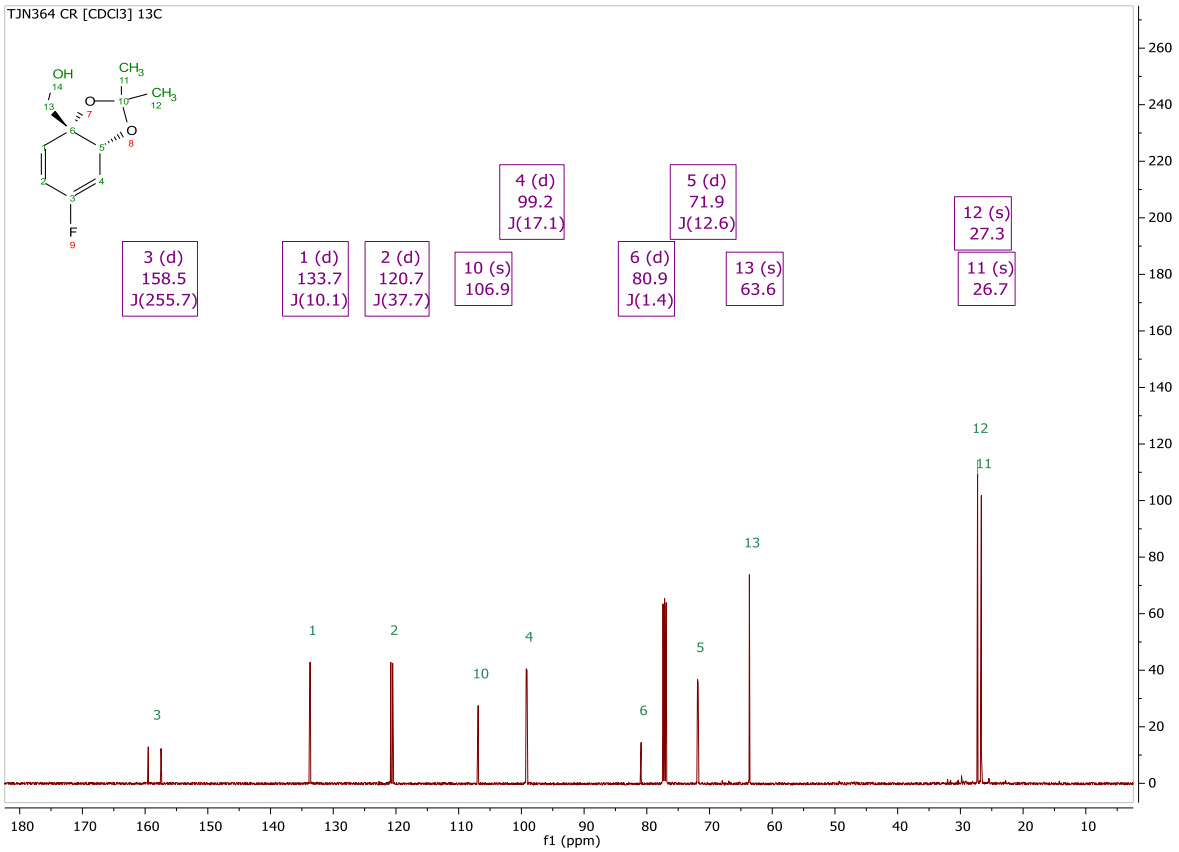
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

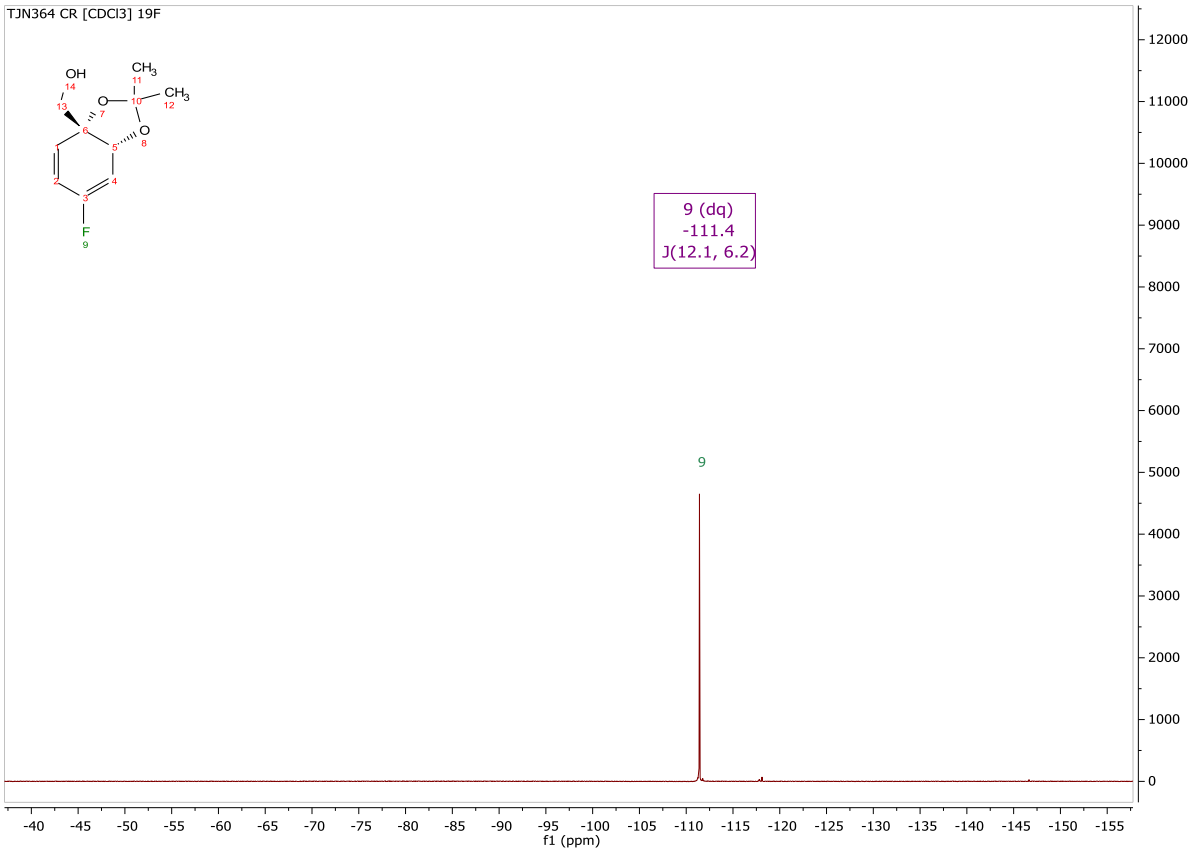


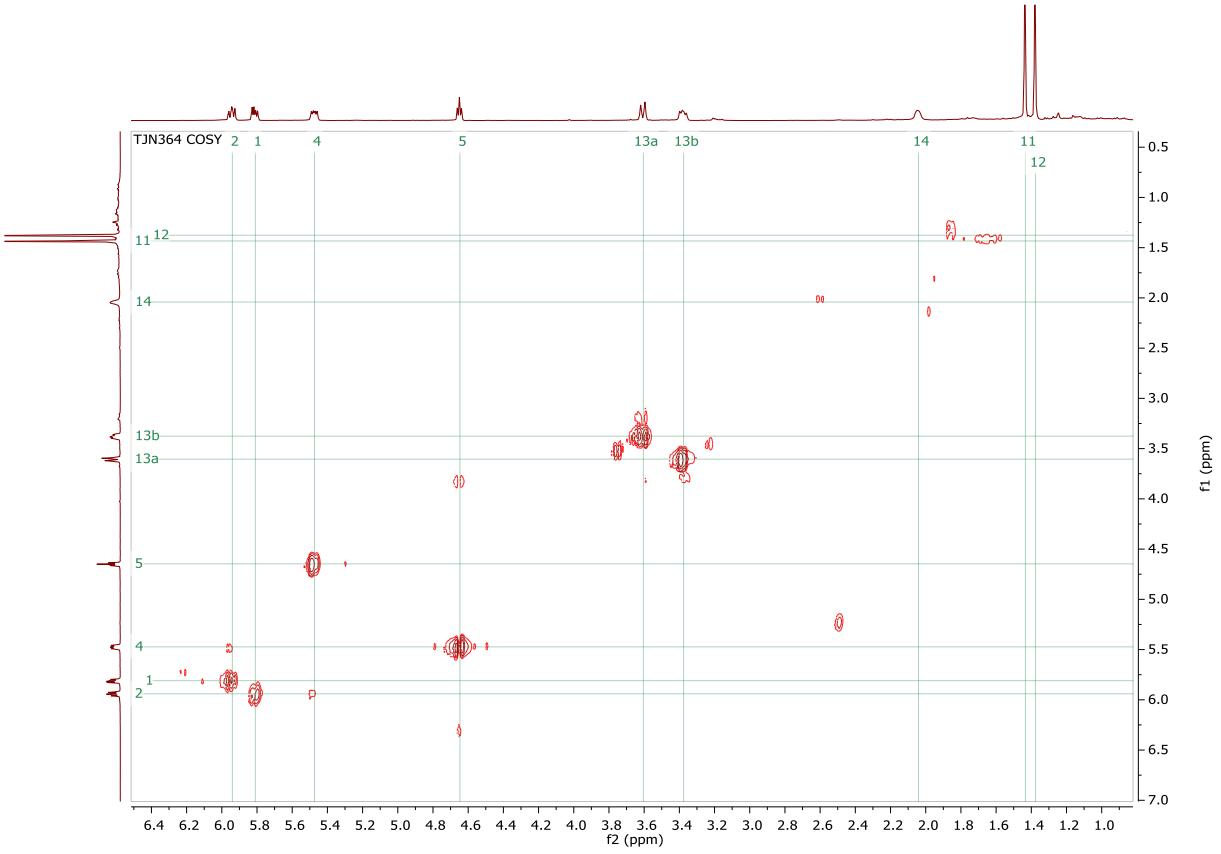
#	m/z	I	I %	Area	S/N
1	142.1583	7948	100.0	211	11140.9
2	233.1528	3498	44.0	158	1194.0
3	236.0755	3596	45.2	129	1156.7
4	241.1571	6338	79.7	289	1853.2
5	251.0707	5254	66.1	267	1304.5
6	259.2068	2680	33.7	133	660.2
7	273.1837	4109	51.7	199	1021.6
8	281.1893	4300	54.1	250	1074.9
9	313.2152	5705	71.8	317	1297.2
10	353.2468	5410	68.1	322	1051.8

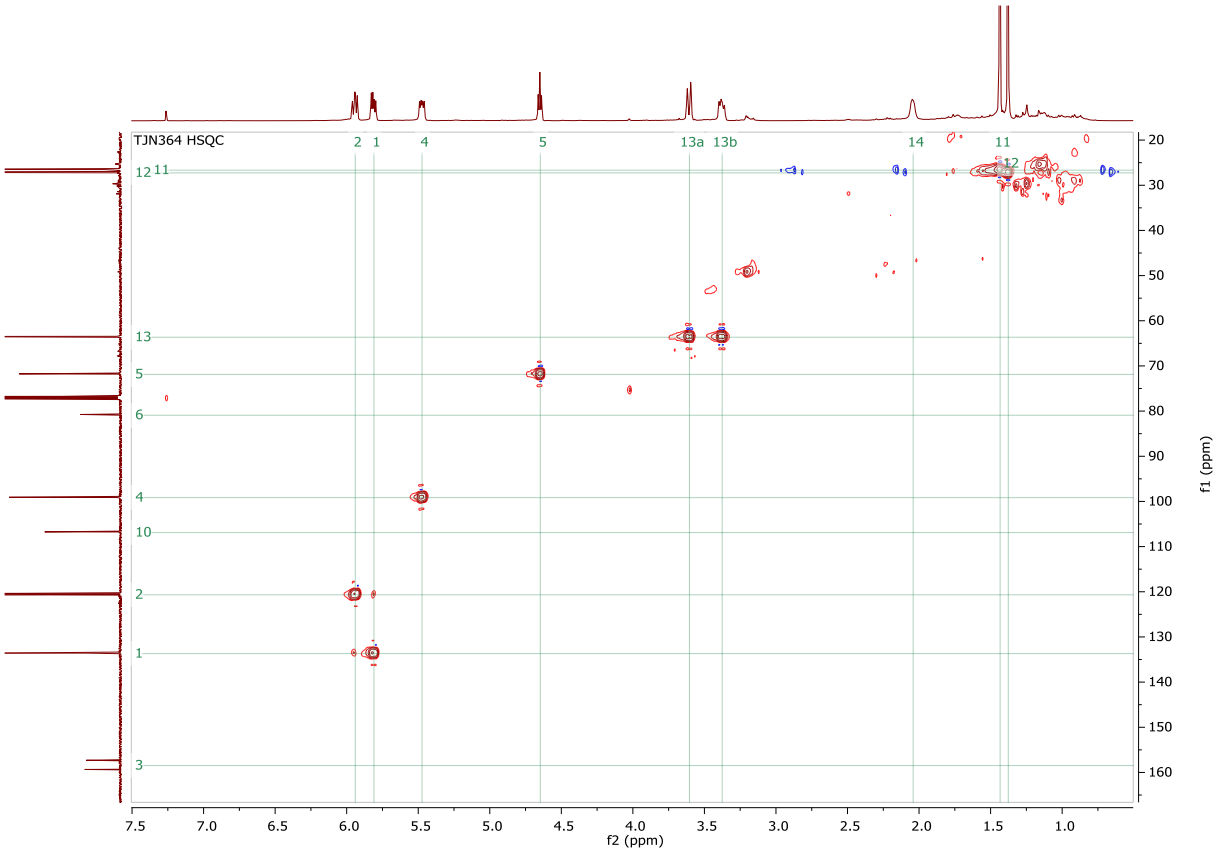
((3a*R*,7a*R*)-6-Fluoro-2,2-dimethylbenzo[d][1,3]dioxol-3a(7aH)-yl)methanol IV-31

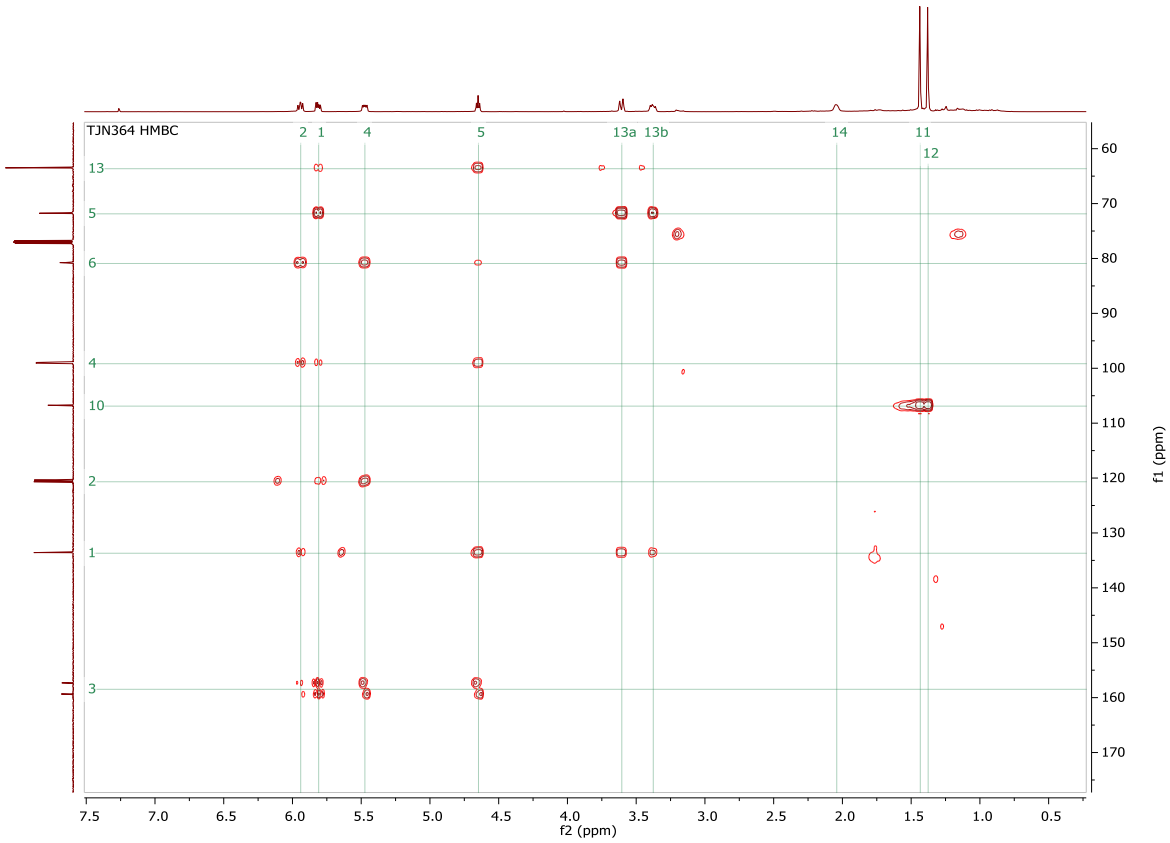





TJN364 CR [CDCl3] 19F
OH
14
CH3
11
CH3
12
O
7
10
O
8
13
6
5
1
2
4
3
F
9
9 (dq)
-111.4
J(12.1, 6.2)
9
f1 (ppm)


TJN364 COSY
2
1
4
5
13a
13b
14
11
12
f2 (ppm)
f1 (ppm)


TJN364 HSQC
2 1 4 5 13a 13b 14 11 12
12 11
13
5
6
4
10
2
1
3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160
f1 (ppm)

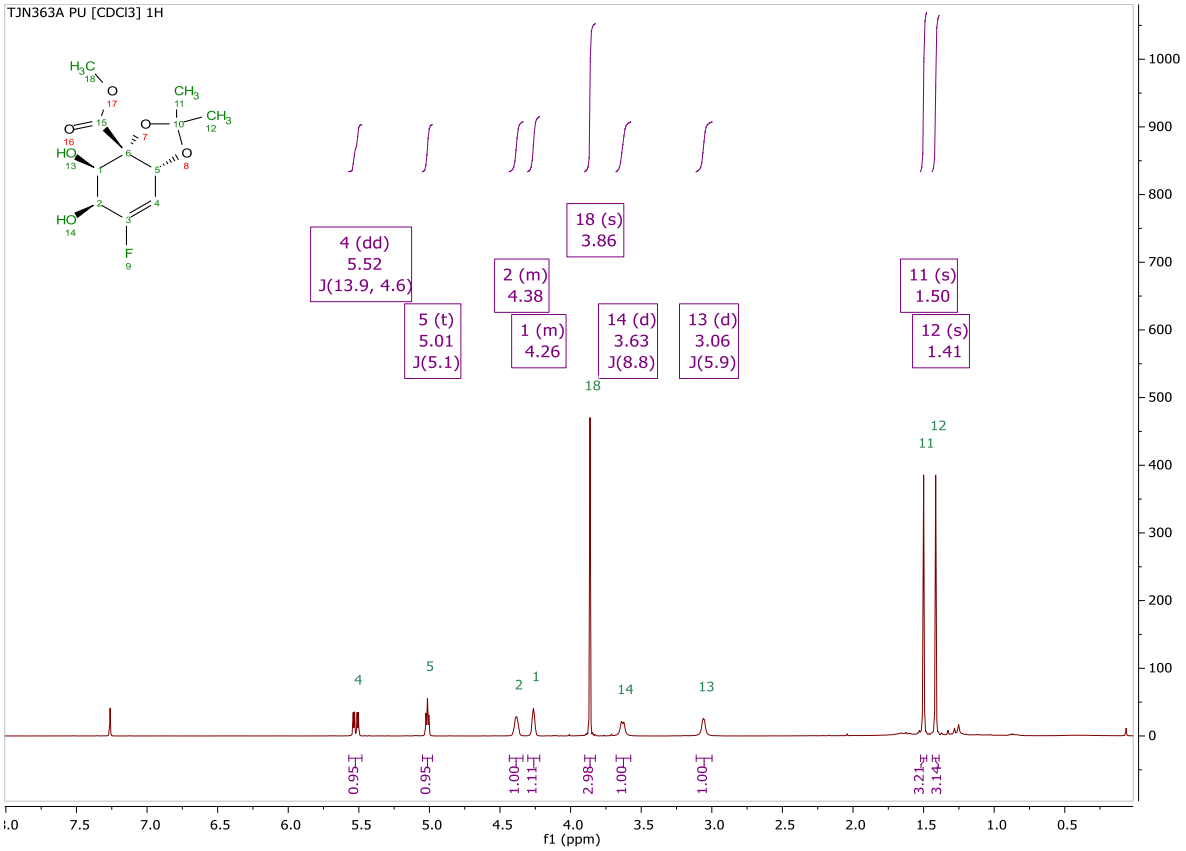

TJN364 HMBC
2 1 4 5 13a 13b 14 11 12
13
5
6
4
10
2
1
3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)
60 70 80 90 100 110 120 130 140 150 160 170
f1 (ppm)

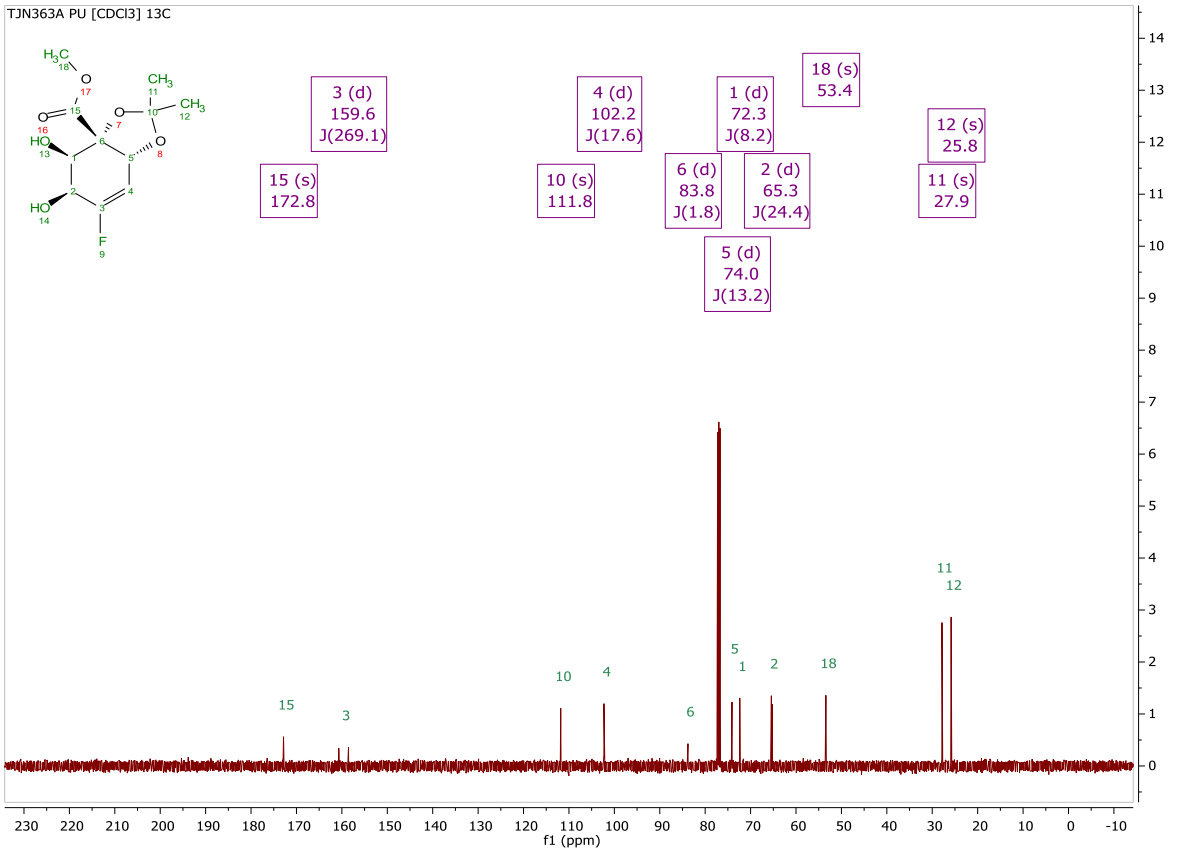
Bruker Daltonics Compass OpenAccess 1.3.0 - Results of job 71878 - Wed Aug 02 16:34:17 BST 2017

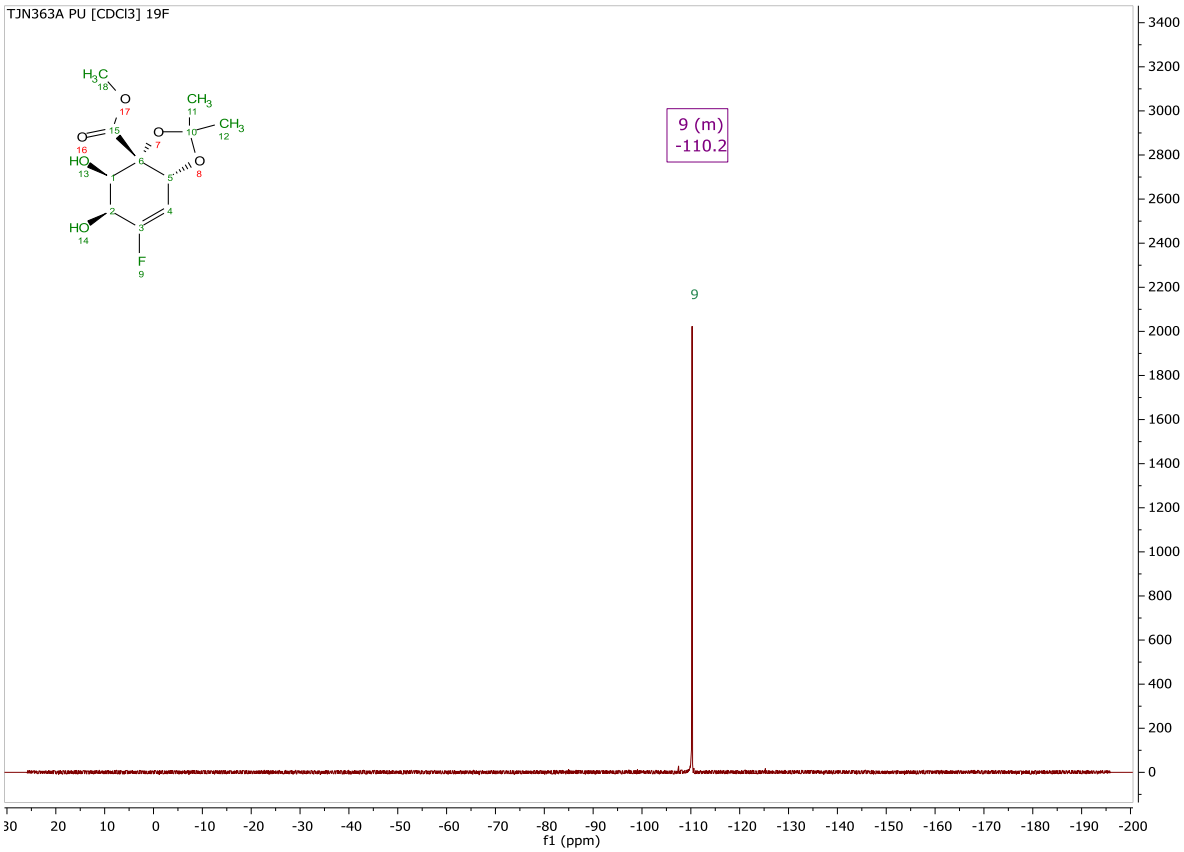
Results of job 71878

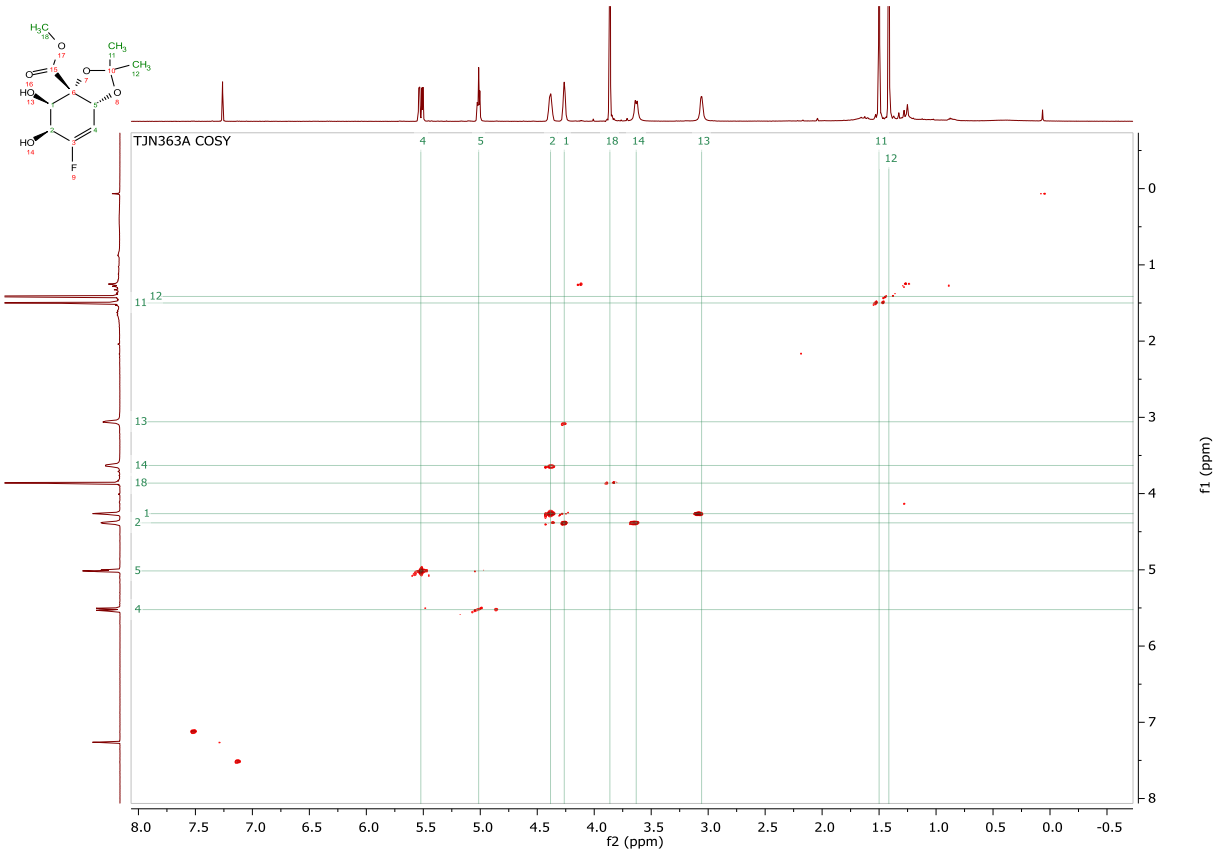
Sample	Sample Description	Method	Submitter	Pos	Expected Formula	Project	Peaknumber	meas. m/z	theo. m/z	err[ppm]	sigma	Formulae
tn_sel_TJN395		Confirm Formula Positive 50to500 loop inj	tjn30 Toby Nash		C10 H13 O3 F1	TJN395	1	223.073500	223.0741	-2.7	0.0253	C 10 H 13 F 1 Na 1 O 3

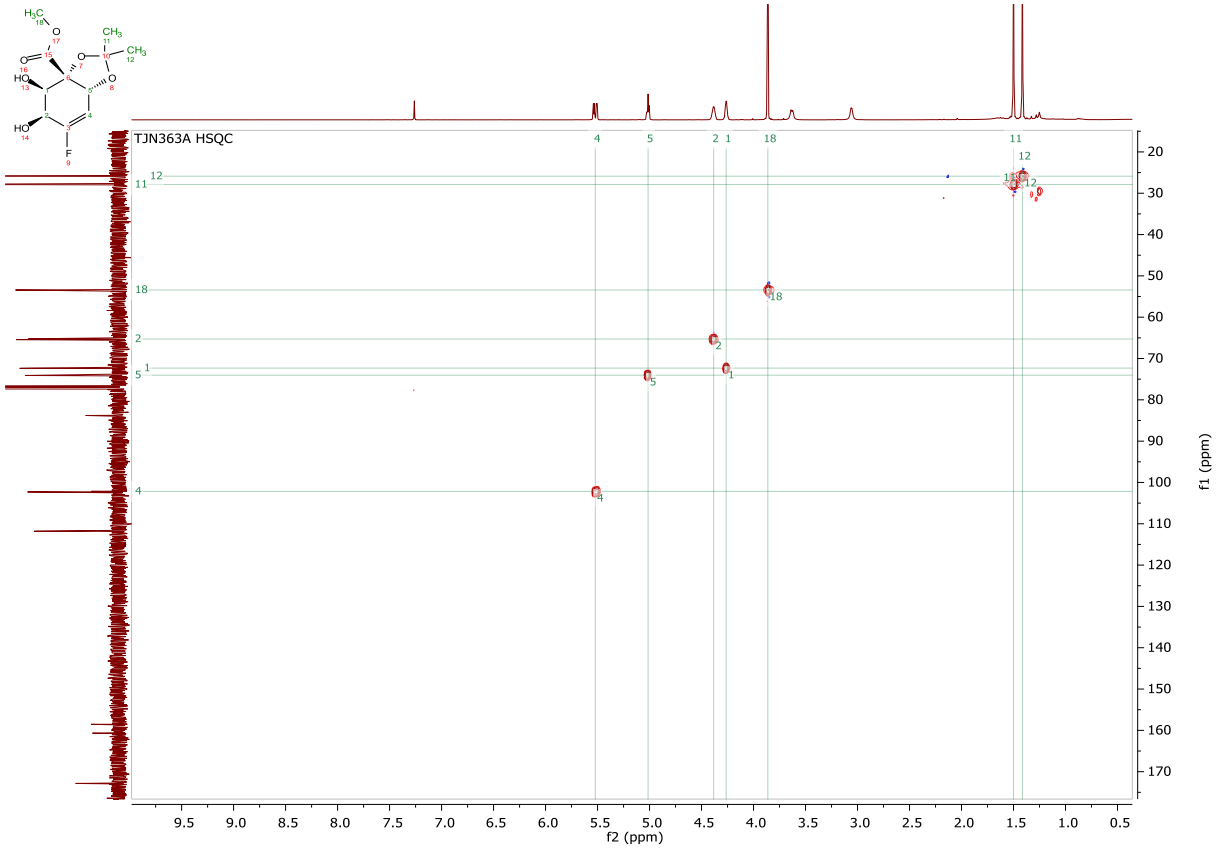
Methyl (3a*S*,4*R*,5*S*,7a*R*)-6-fluoro-4,5-dihydroxy-2,2-dimethyl-5,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-32

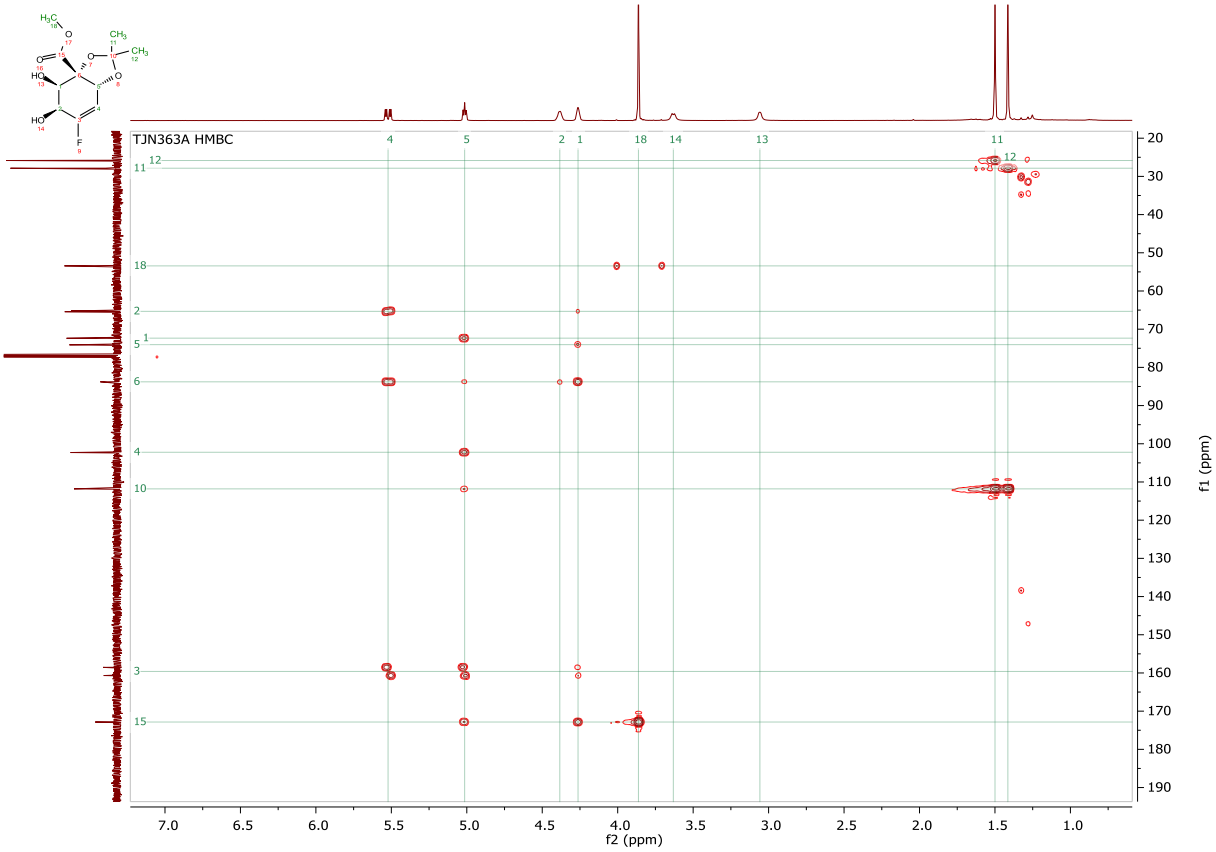





TJN363A PU [CDCl3] 19F
9 (m)
-110.2
9
f1 (ppm)


TJN363A COSY
f2 (ppm)
f1 (ppm)

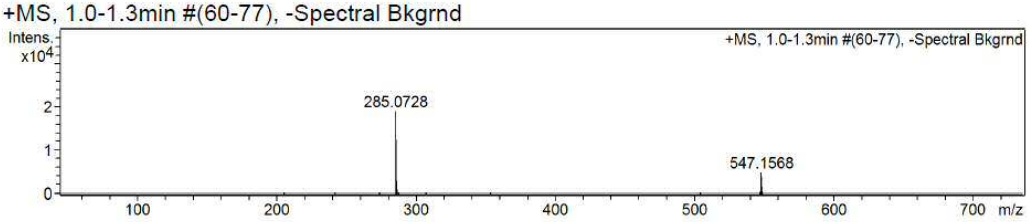

TJN363A HSQC
f2 (ppm)
f1 (ppm)


TJN363A HMBC
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

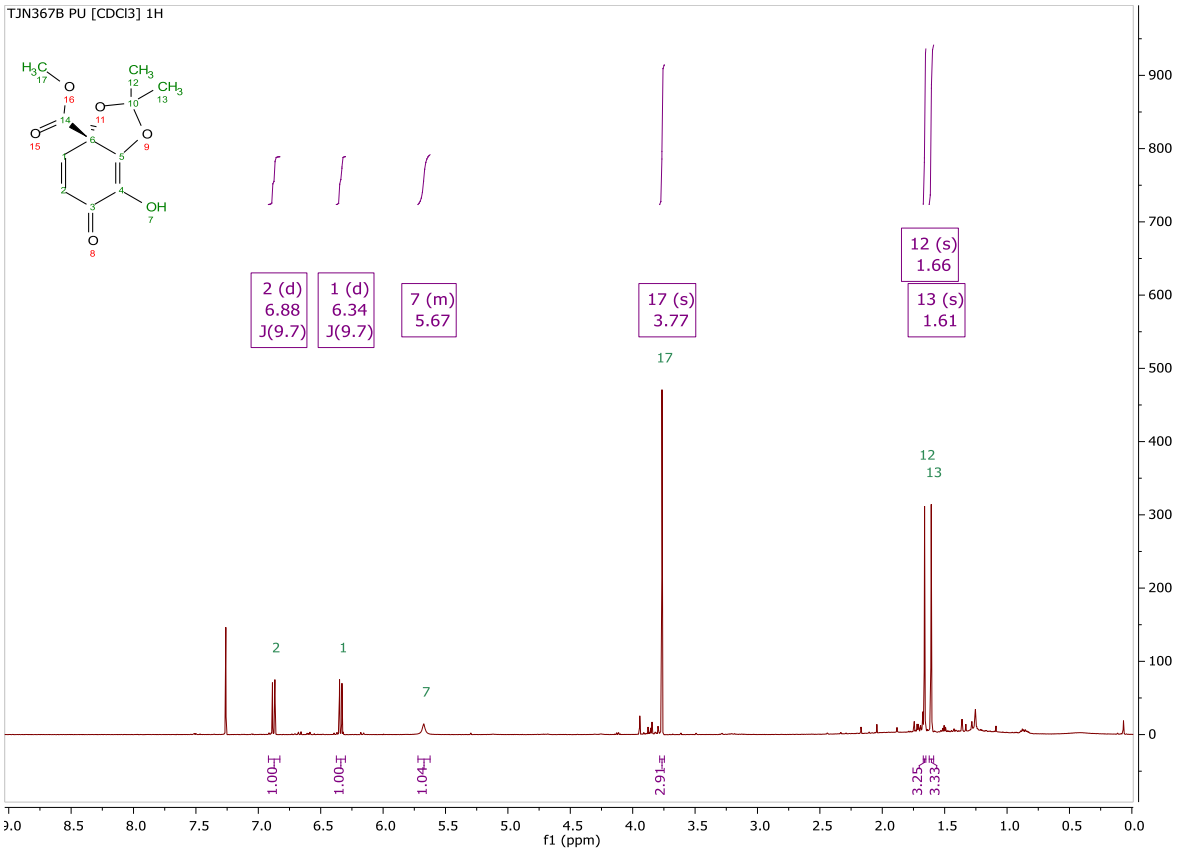
Sample-ID	tn_sel_TJN363A	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN363A_352166_28_01_57668.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	08/05/2017 14:36:40
Ionisation Mode	positive electrospray (ESI)		

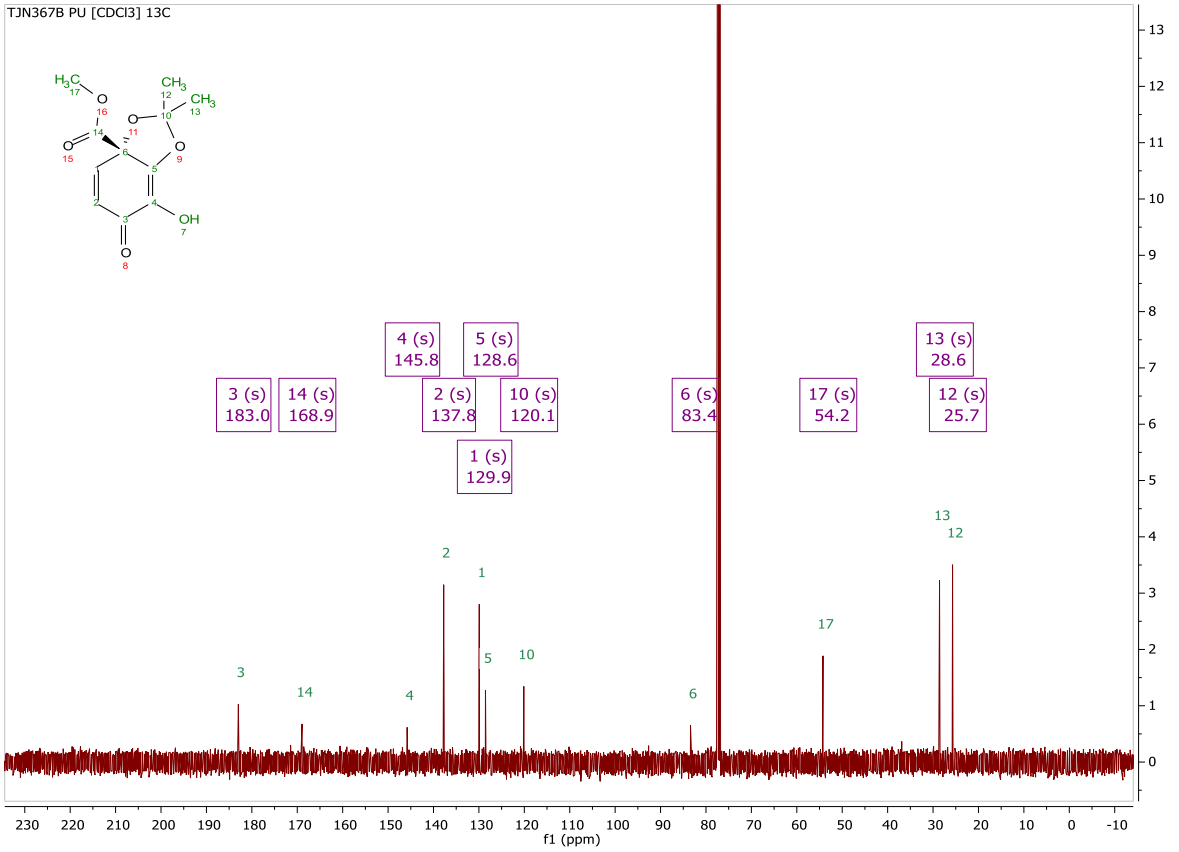
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

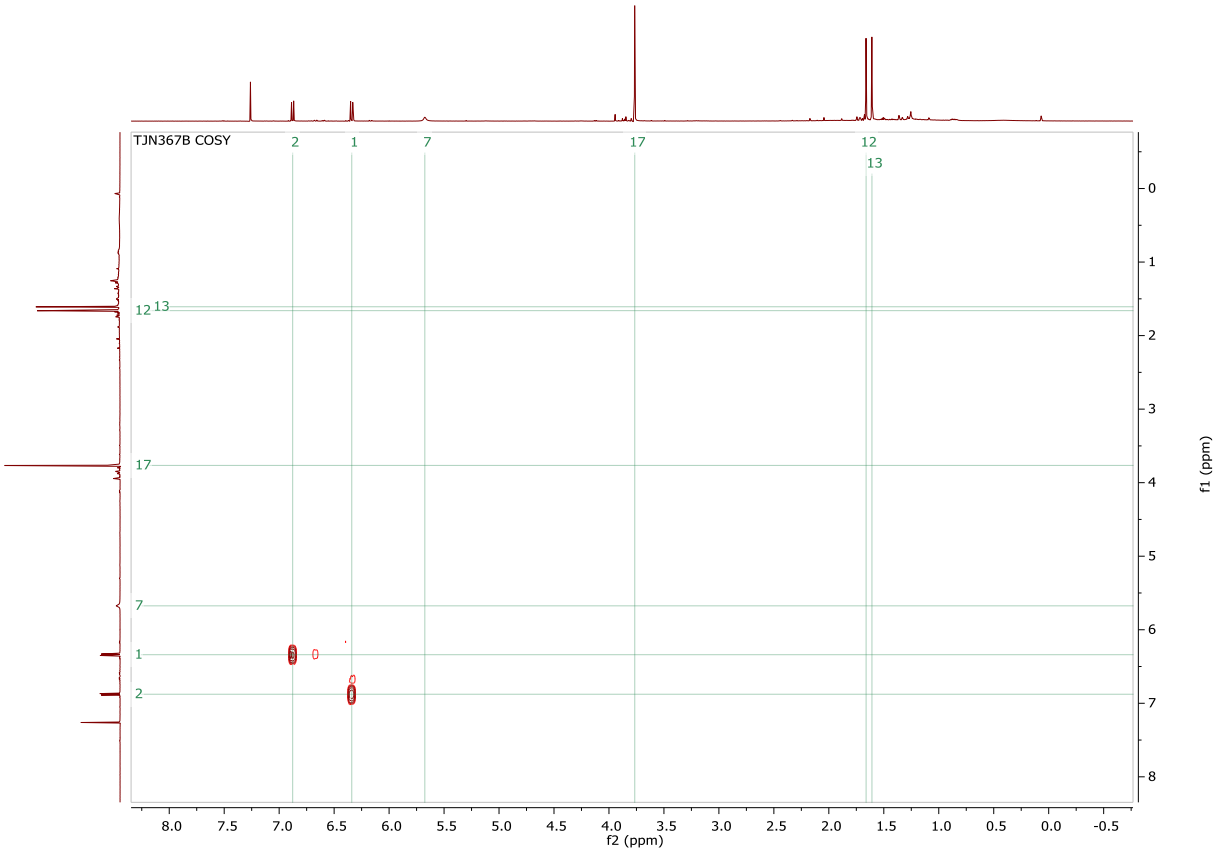


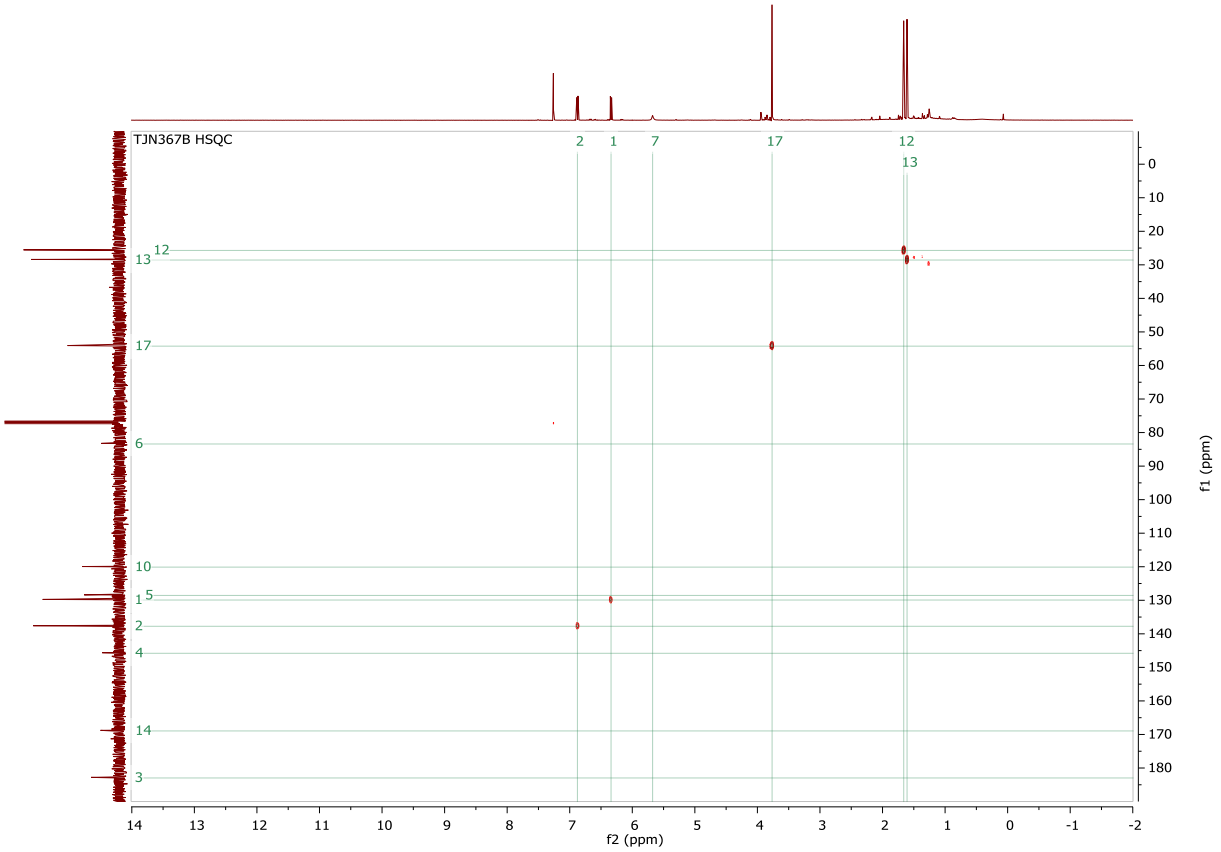
#	m/z	I	I %	Area	S/N
1	205.0504	302	1.6	12	271.6
2	242.1014	259	1.4	7	209.9
3	274.0752	295	1.6	12	149.5
4	285.0728	18924	100.0	959	8148.0
5	286.0786	1516	8.0	87	643.7
6	307.0568	205	1.1	13	79.4
7	353.0619	353	1.9	25	170.5
8	504.1849	372	2.0	28	123.8
9	547.1568	4885	25.8	491	1307.1
10	548.1602	818	4.3	94	218.9

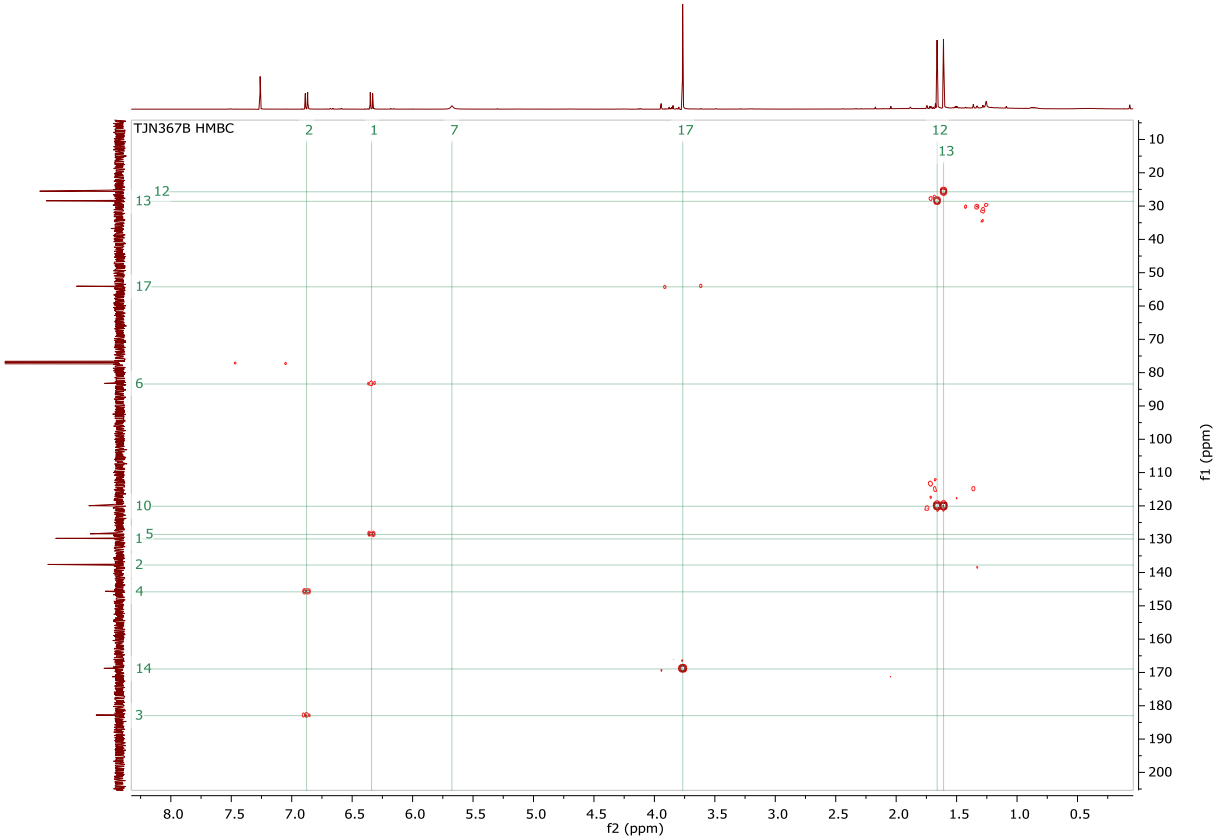
Methyl (*S*)-7-hydroxy-2,2-dimethyl-6-oxobenzo[d][1,3]dioxole-3a(6H)-carboxylate IV-33






TJN367B COSY
2
1
7
17
12
13
12
13
17
7
1
2
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)
0
1
2
3
4
5
6
7
8
f1 (ppm)

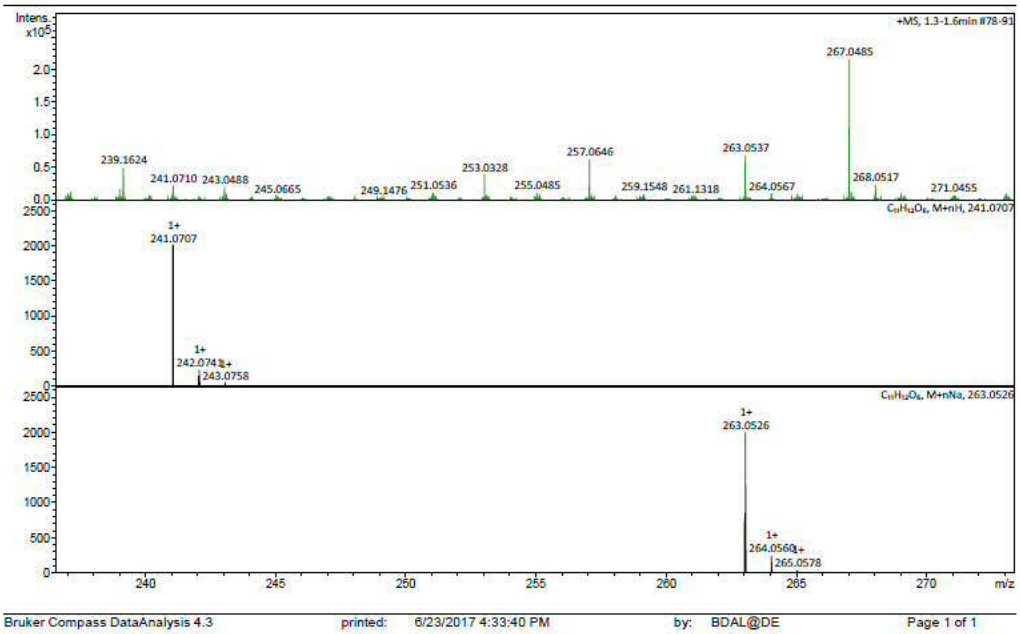

TJN367B HSQC
2
1
7
17
12
13
13
12
17
6
10
15
2
4
14
3
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
f1 (ppm)



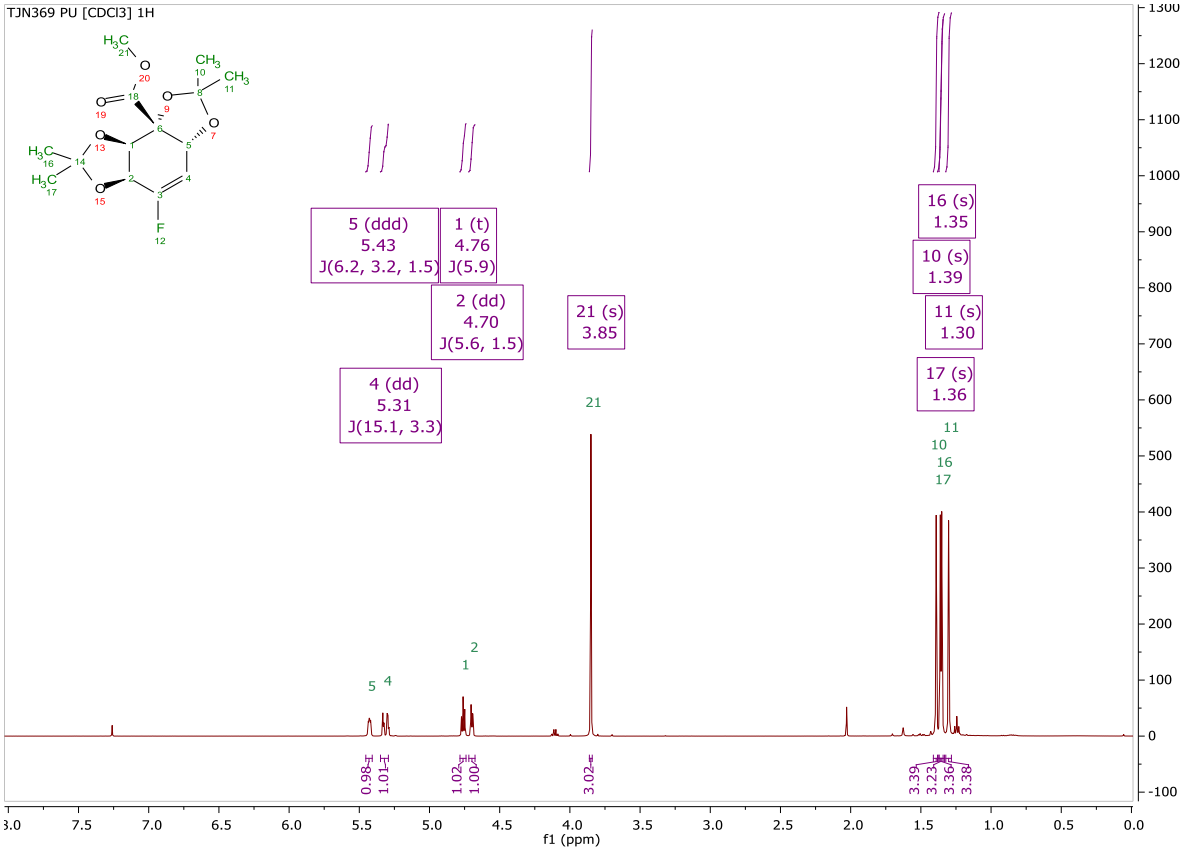
Generic Display Report

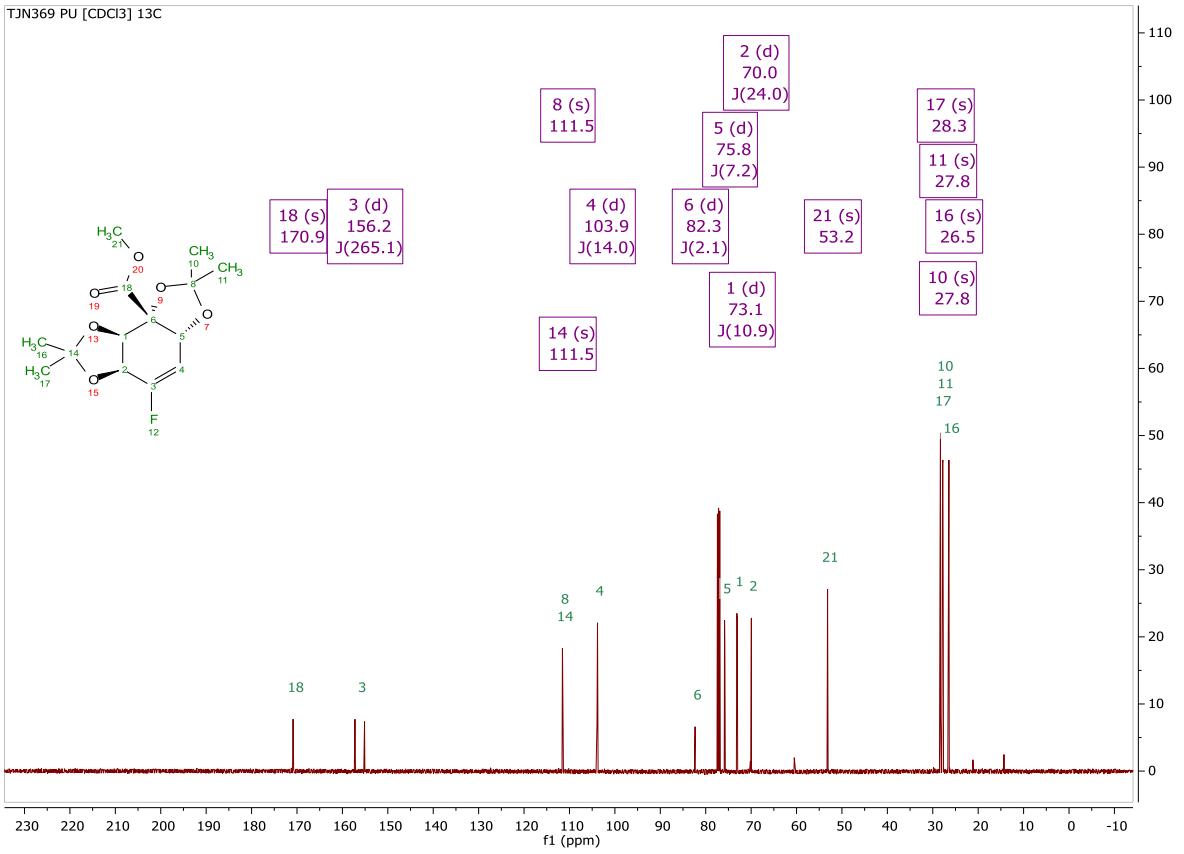
Analysis Info

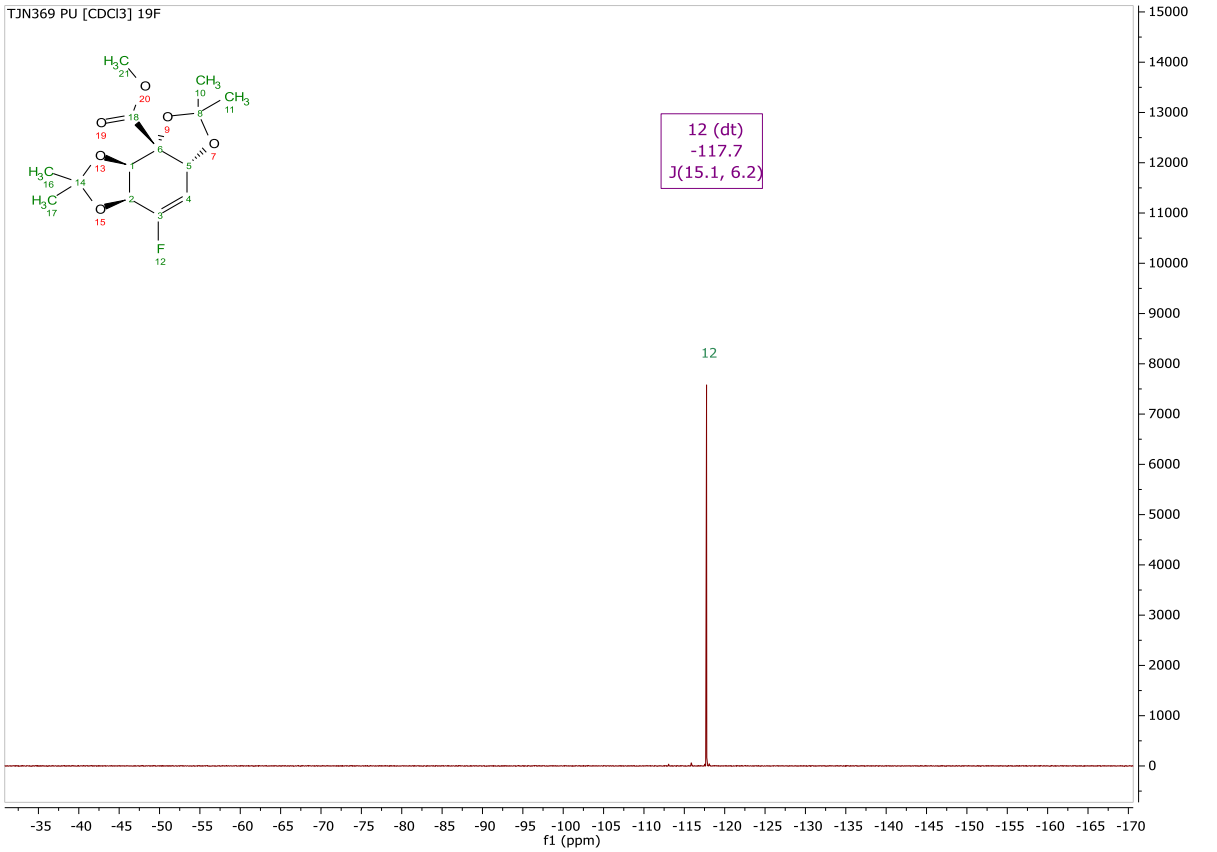
Analysis Name	D:\Data\Anneke\2017-06-21 Open Access\TJN367B_RE1_01_13978.d	Acquisition Date	6/23/2017 3:03:47 PM
Method	sbr dan fia pos 75 -1000.m	Operator	BDAL@DE
Sample Name	TJN367B	Instrument	maXis-HD
Comment			

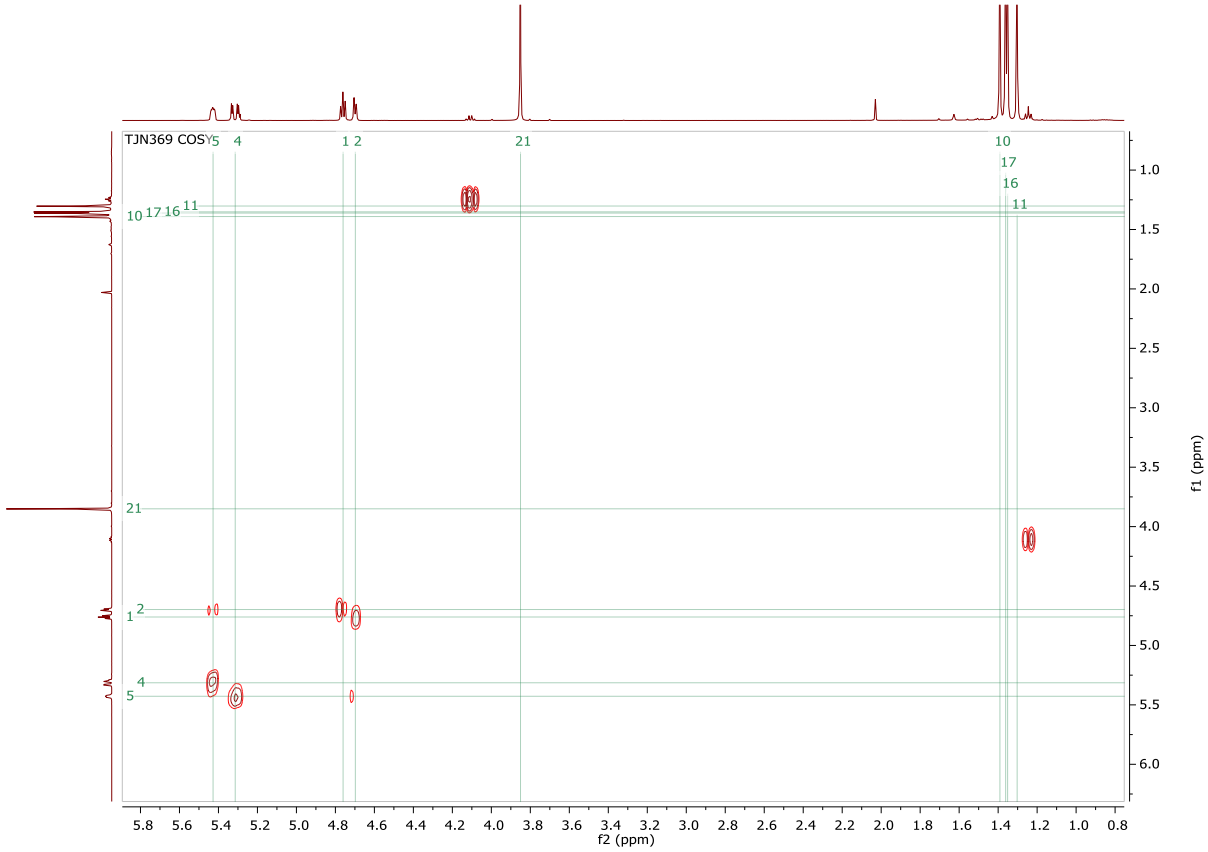


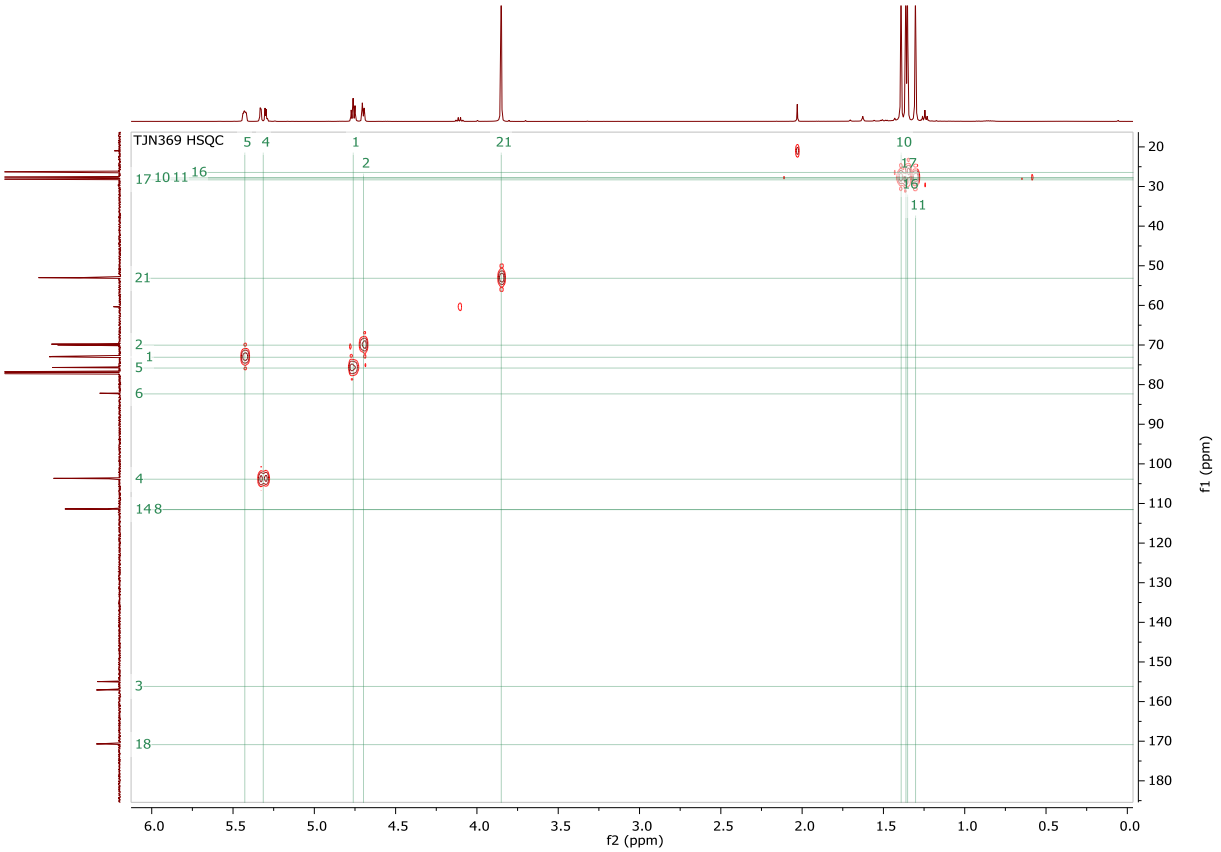
Methyl (3a*S*,5a*R*,8a*R*,8b*R*)-4-fluoro-2,2,7,7-tetramethyl-3a,8b-dihydrobenzo[1,2-d:3,4-d']bis([1,3]dioxole)-8a(5aH)-carboxylate IV-35

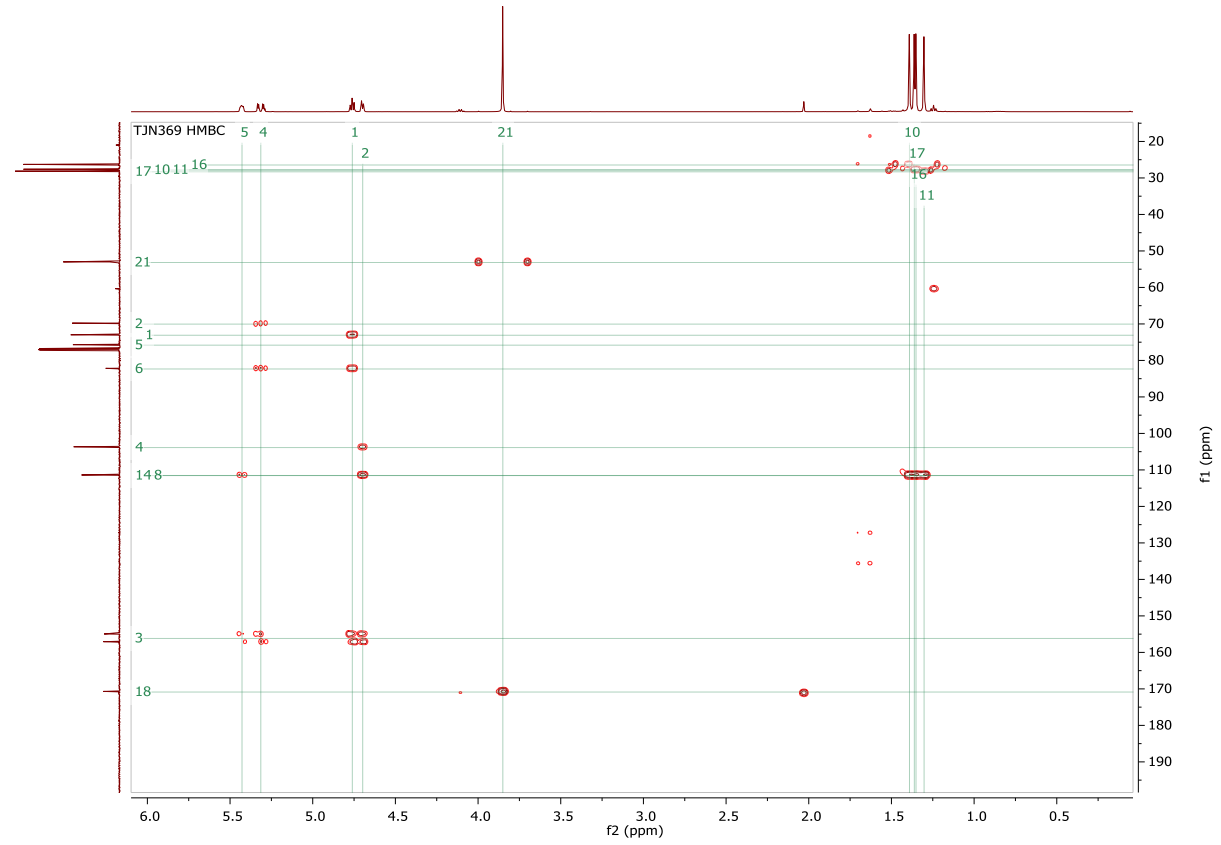





TJN369 PU [CDCl3] 19F
12 (dt)
-117.7
J(15.1, 6.2)
12
f1 (ppm)


TJN369 COSY
f2 (ppm)
f1 (ppm)

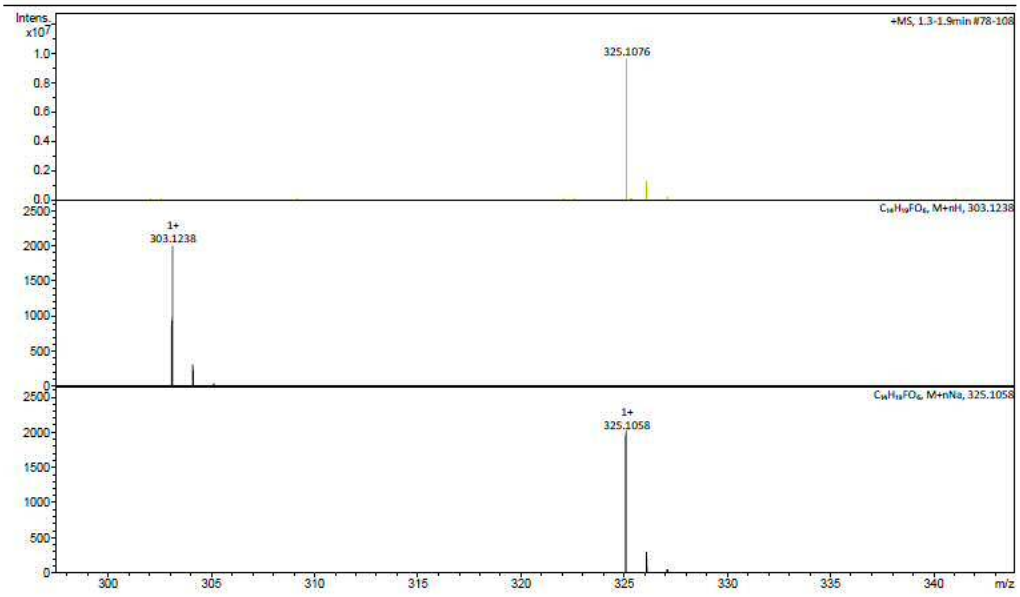

TJN369 HSQC
f2 (ppm)
f1 (ppm)


TJN369 HMBC
f2 (ppm)
f1 (ppm)

Generic Display Report

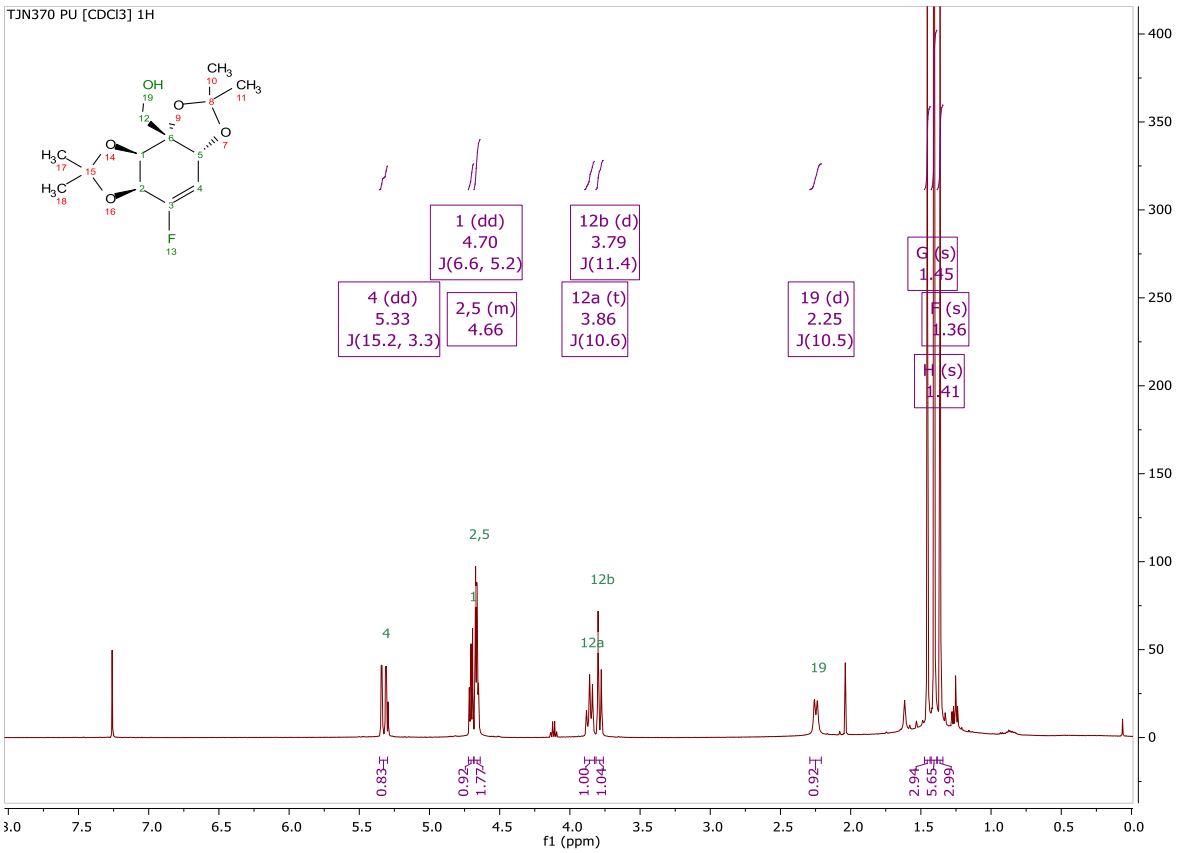
Analysis Info

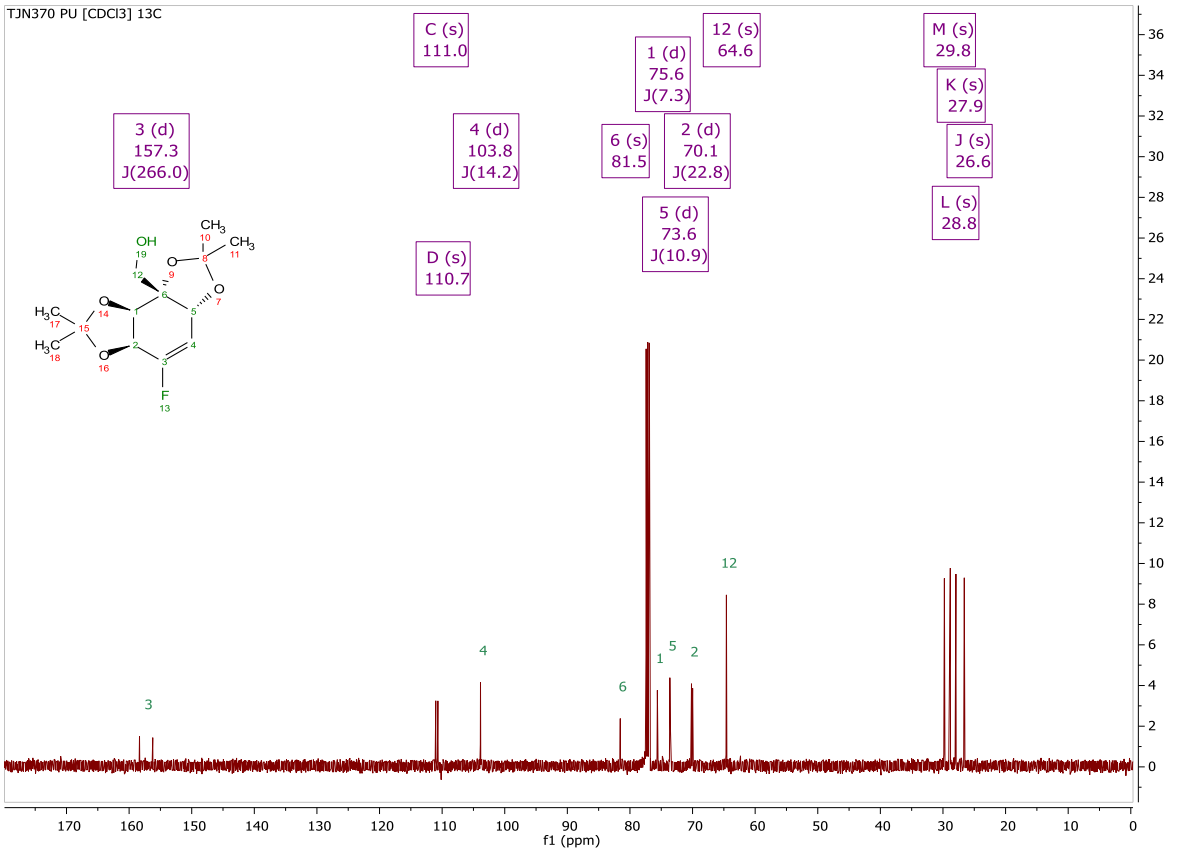
Analysis Name	D:\Data\Anneke\2017-06-21 Open Access\TJN369_RD8_01_13977.d	Acquisition Date	6/23/2017 2:57:32 PM
Method	sbr dan fia pos 75 -1000.m	Operator	BDAL@DE
Sample Name	TJN369	Instrument	maXis-HD
Comment			

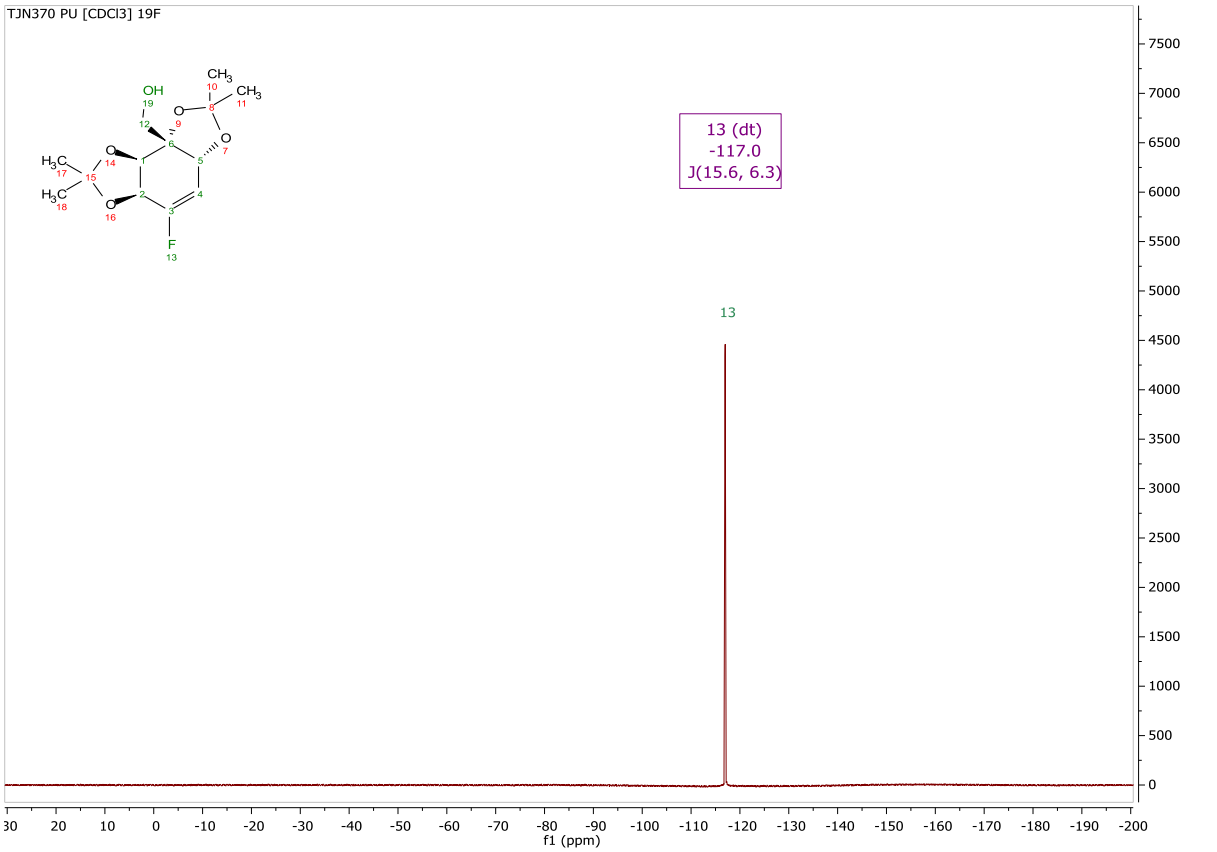


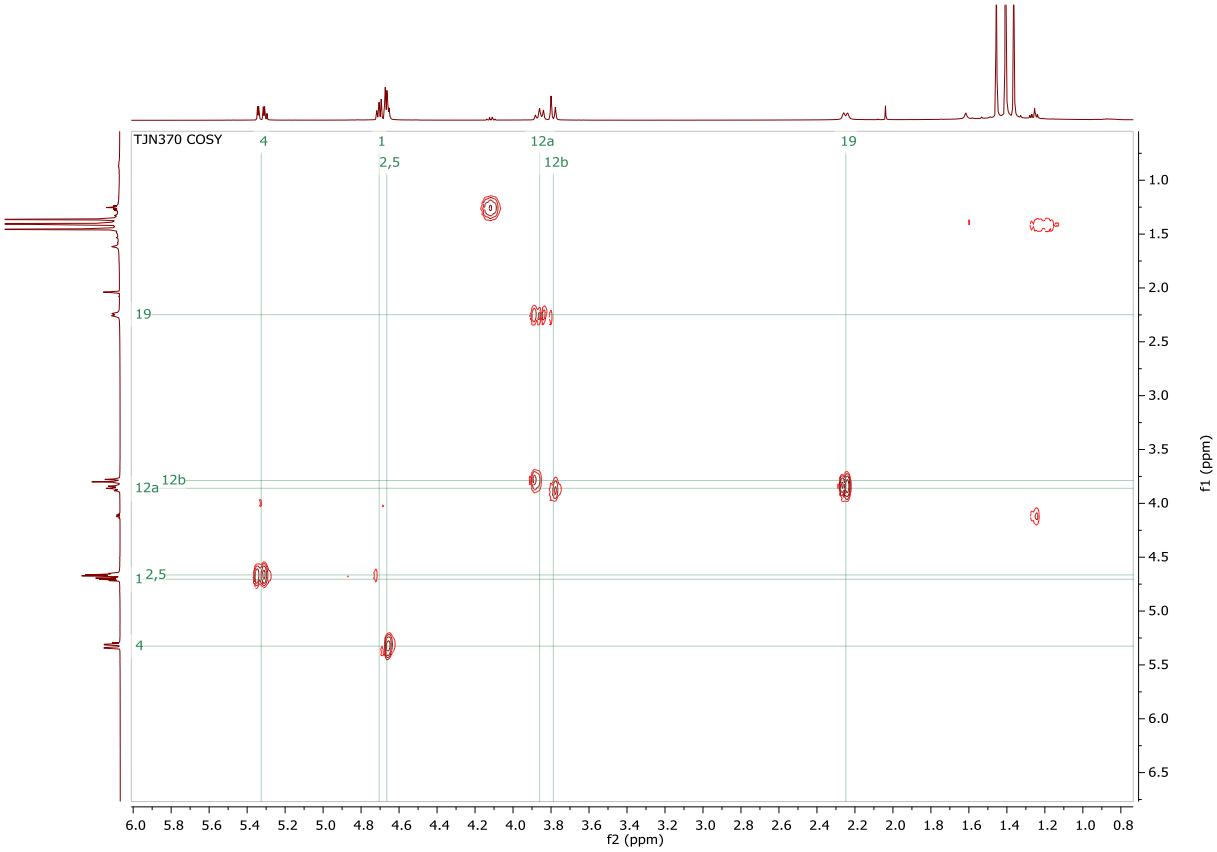
Bruker Compass DataAnalysis 4.3 printed: 6/23/2017 4:35:07 PM by: BDAL@DE Page 1 of 1

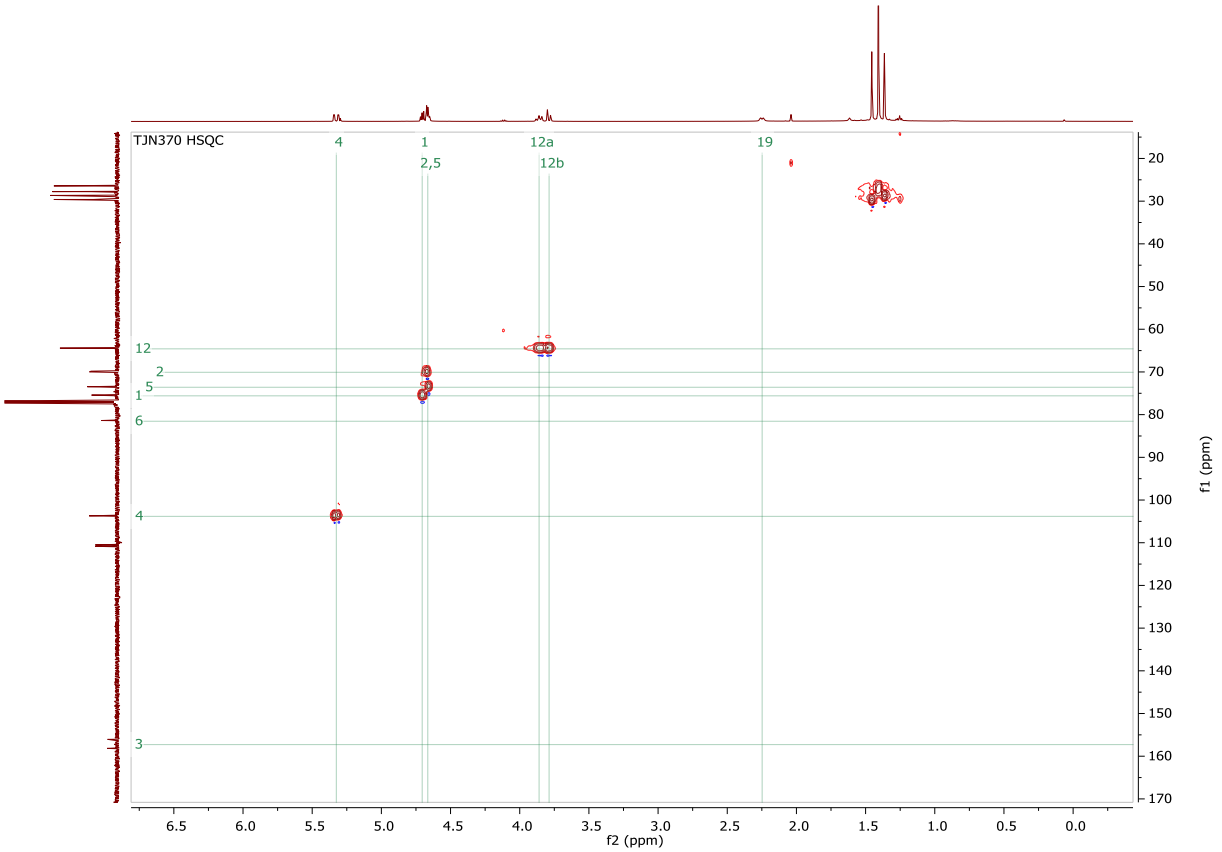
((3a*S*,5a*R*,8a*R*,8b*R*)-4-Fluoro-2,2,7,7-tetramethyl-3a,8b-dihydrobenzo[1,2-d:3,4-d']bis([1,3]dioxole)-8a(5aH)-yl)methanol IV-36

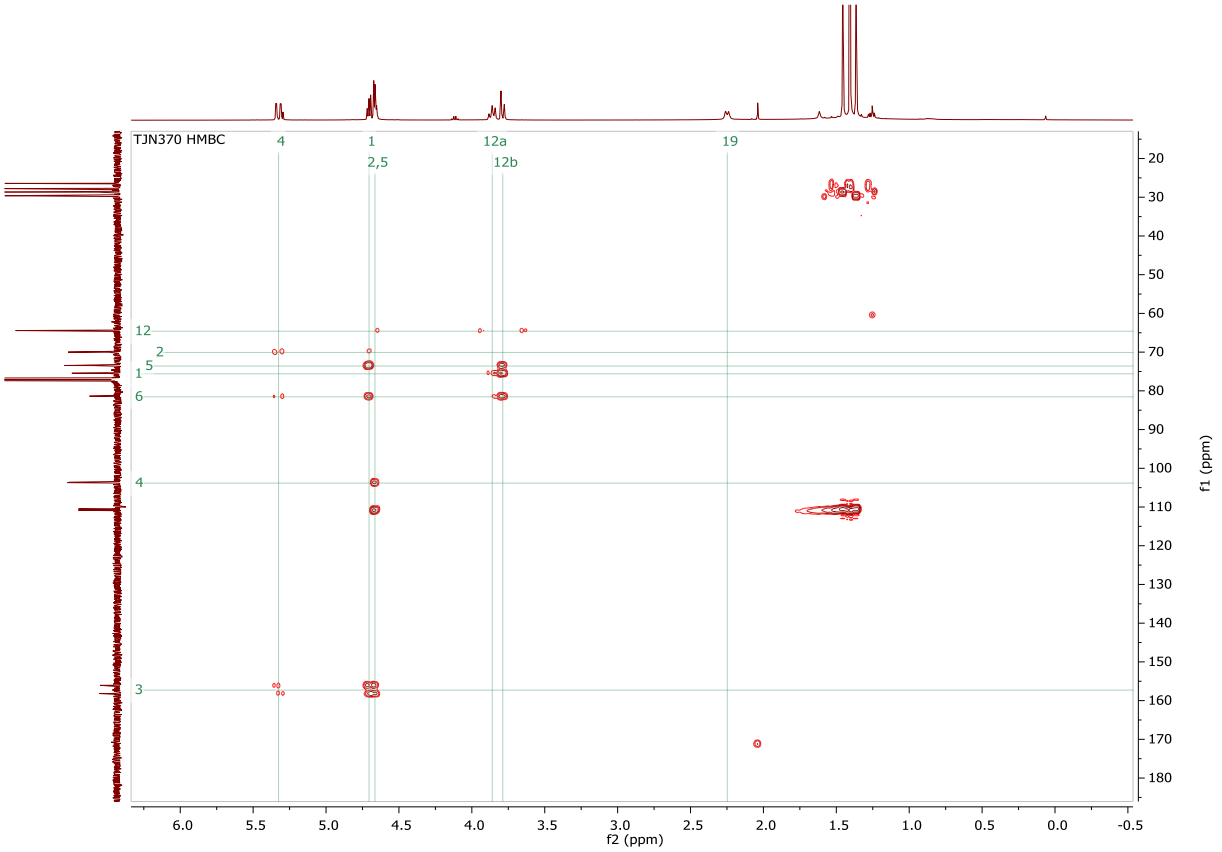





TJN370 PU [CDCl3] 19F
13 (dt)
-117.0
J(15.6, 6.3)
13
f1 (ppm)


TJN370 COSY
4
1
2,5
12a
12b
19
f2 (ppm)
f1 (ppm)

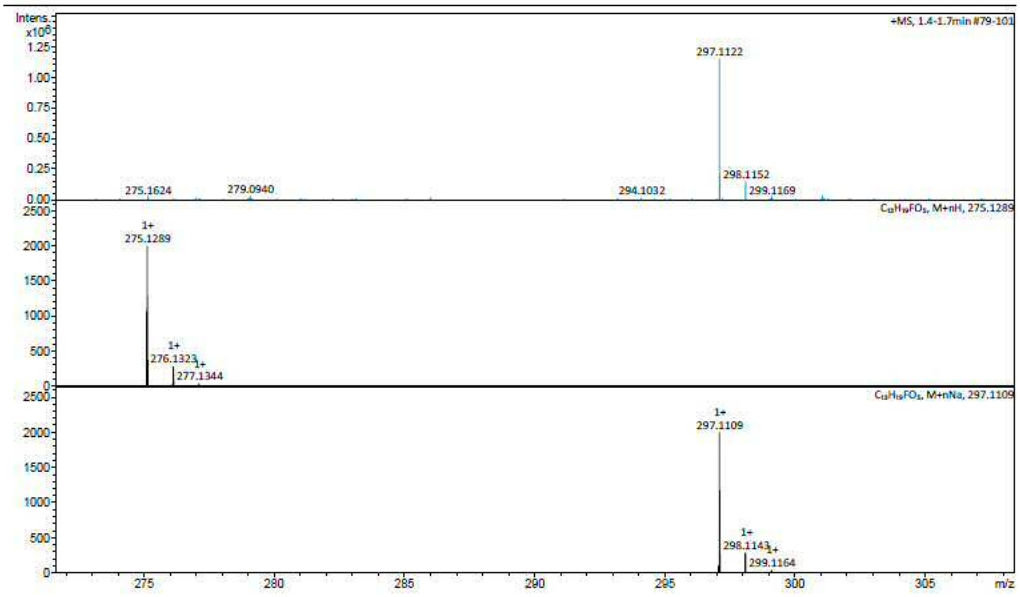

TJN370 HSQC
4
1
2,5
12a
12b
19
12
2
1
5
6
4
3
f2 (ppm)
f1 (ppm)


TJN370 HMBC
4
1
2,5
12a
12b
19
12
2
1
5
6
4
3
f2 (ppm)
f1 (ppm)

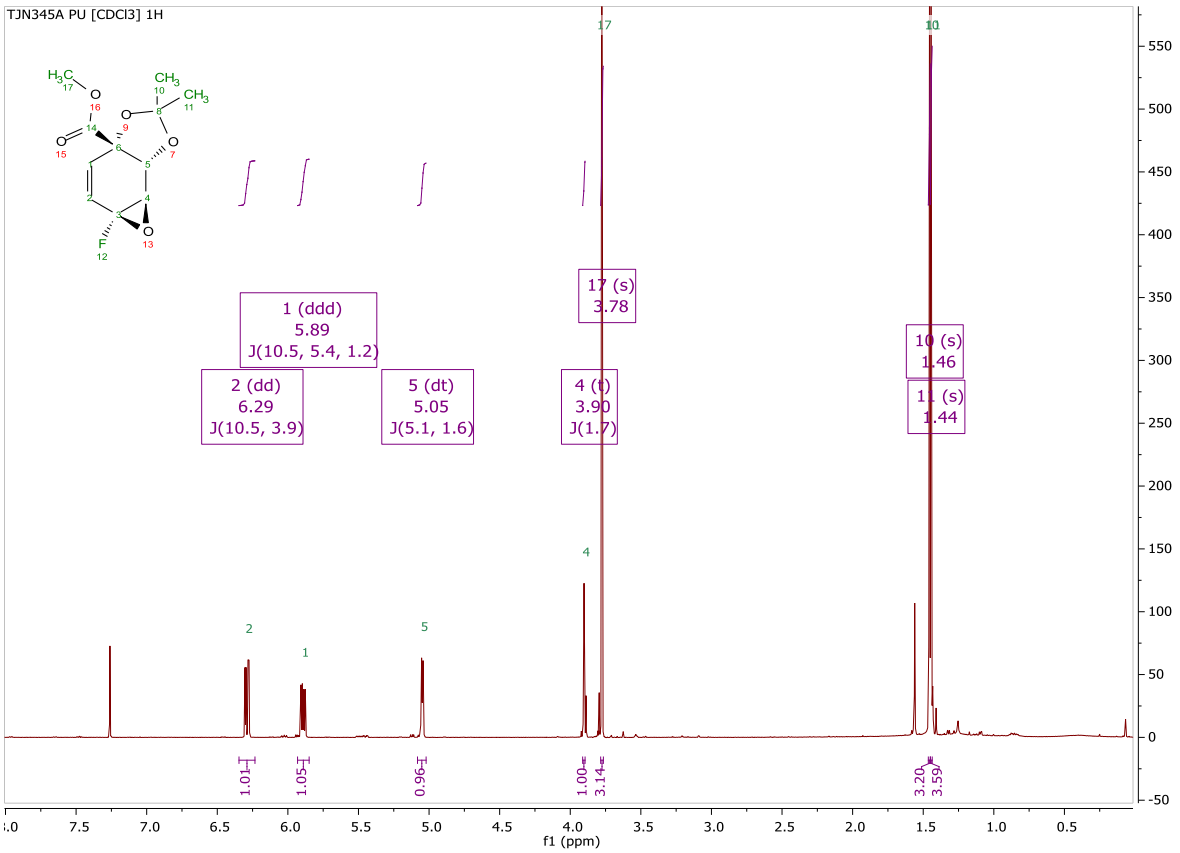
Generic Display Report

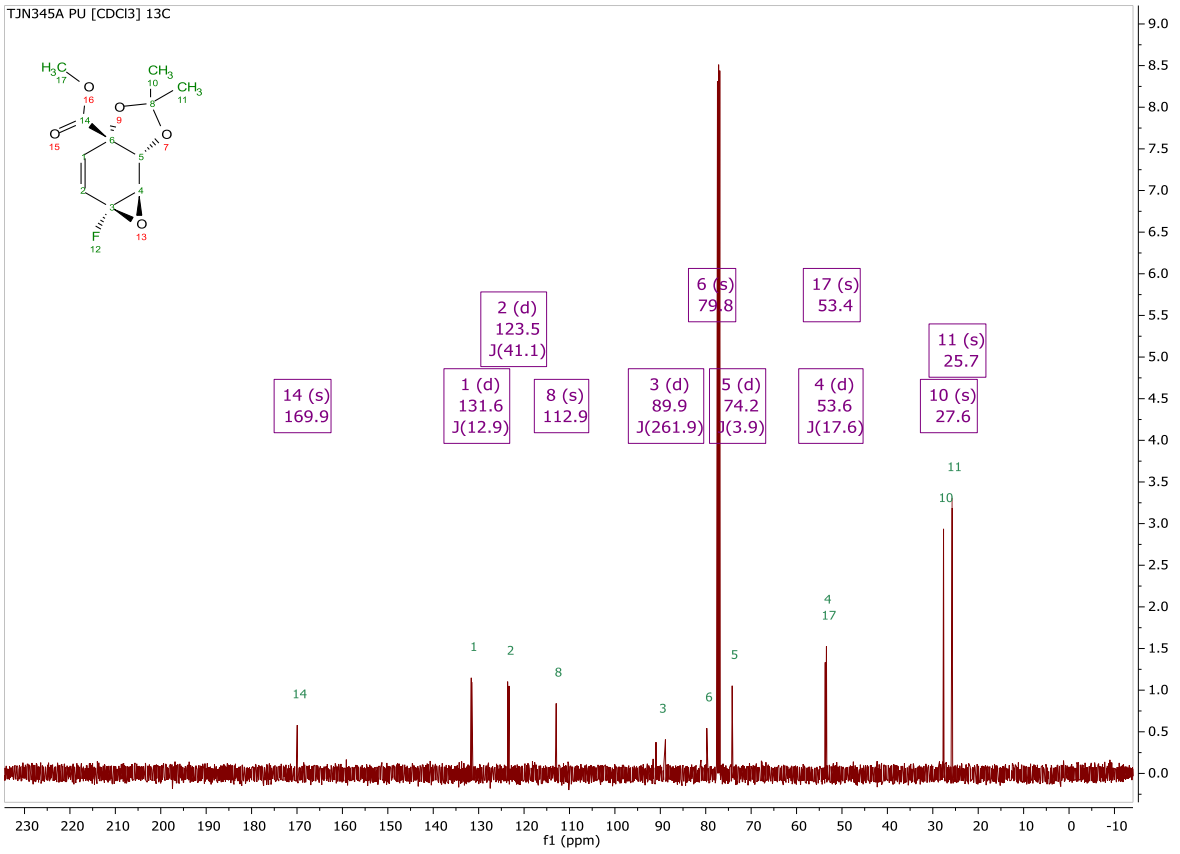
Analysis Info

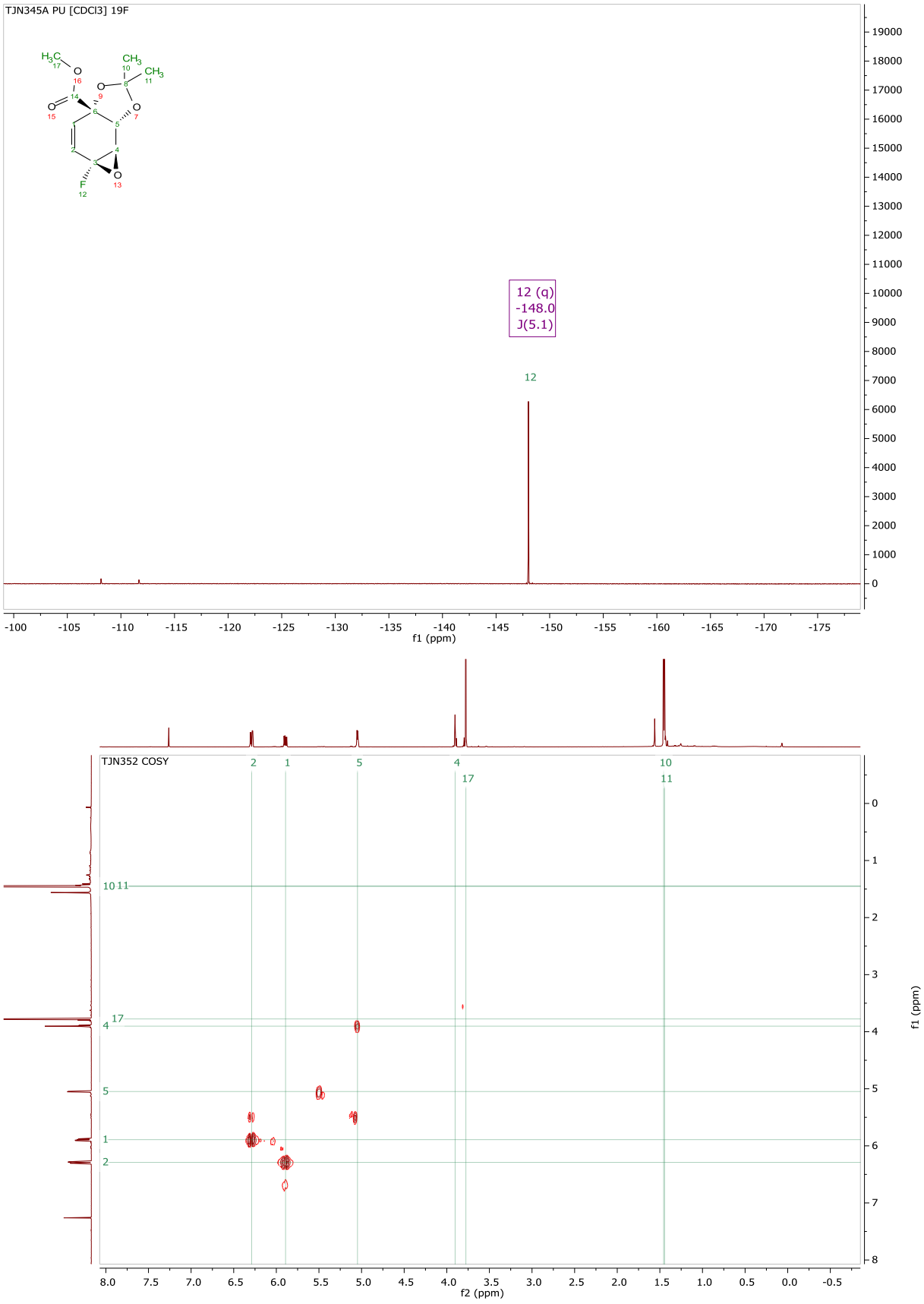
Analysis Name	D:\Data\Anneke\2017-06-21 Open Access\TJN370_RE2_01_13979.d	Acquisition Date	6/23/2017 3:10:05 PM
Method	sbr dan fia pos 75 -1000.m	Operator	BDAL@DE
Sample Name	TJN370	Instrument	maXis-HD
Comment			

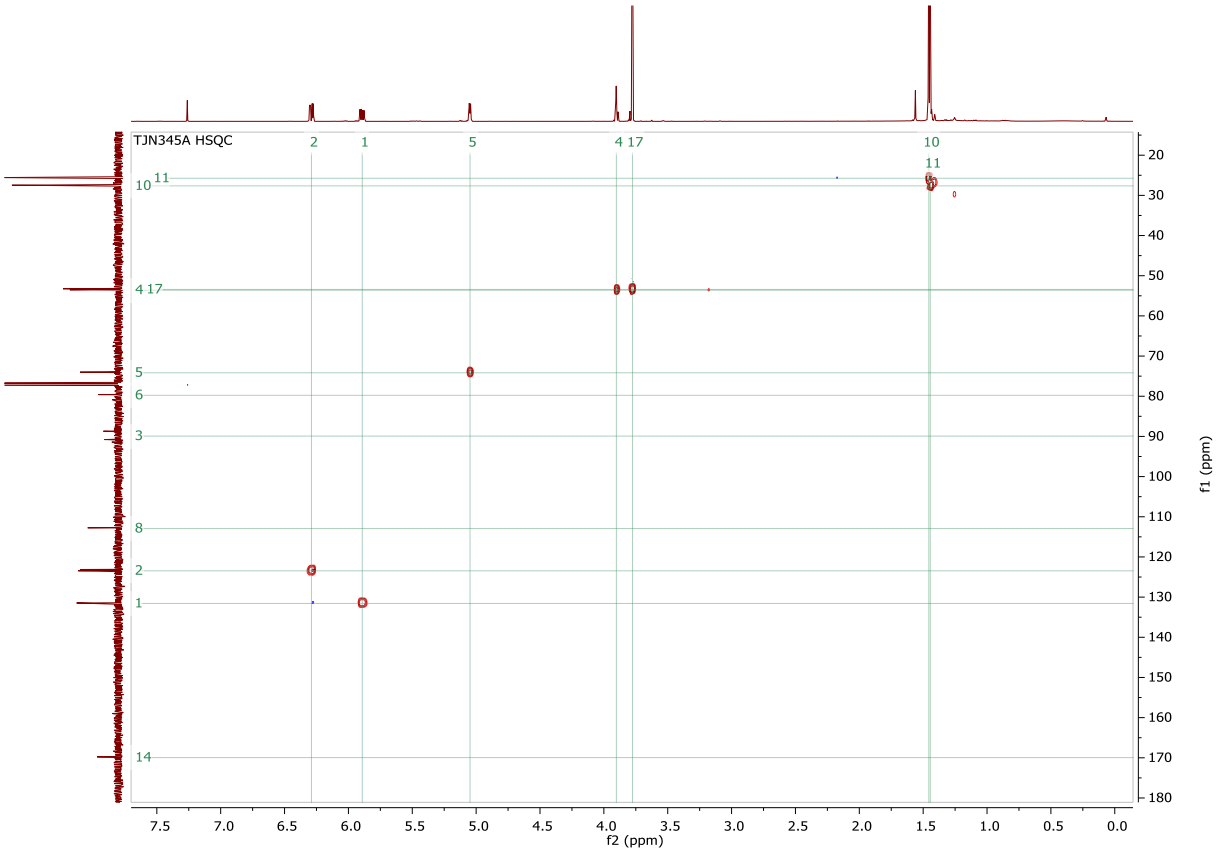


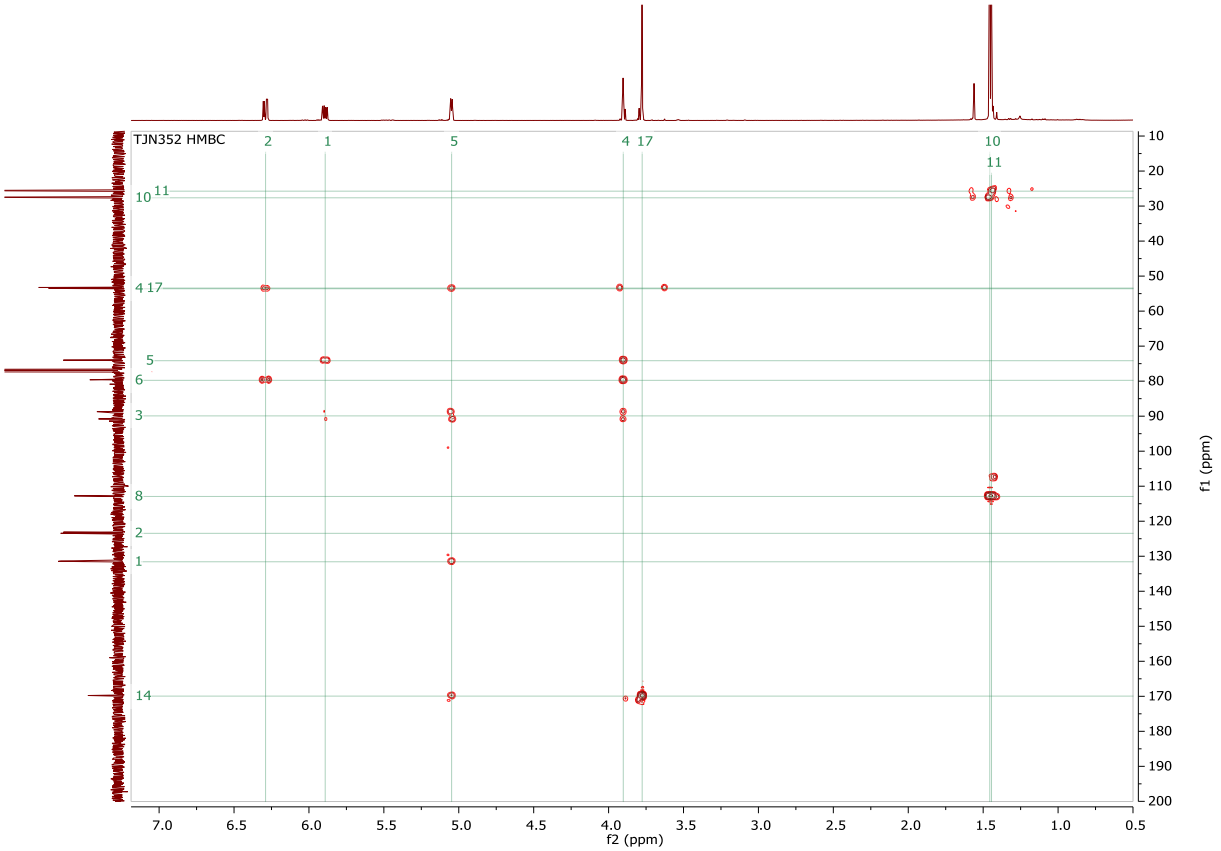
Methyl (3a*S*,5a*R*,6a*R*,6b*R*)-5a-fluoro-2,2-dimethyl-6a,6b-dihydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxole-3a(5aH)-carboxylate IV-38






TJN345A PU [CDCl3] 19F
12 (q)
-148.0
J(5.1)
12
f1 (ppm)
TJN352 COSY
2
1
5
4
17
10
11
f2 (ppm)
f1 (ppm)

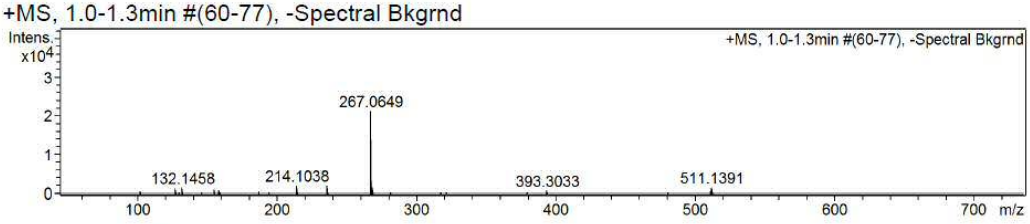

TJN345A HSQC
2
1
5
4 17
10
11
10 11
4 17
5
6
3
8
2
1
14
f2 (ppm)
f1 (ppm)


TJN352 HMBC
2
1
5
4 17
10
11
10 11
4 17
5
6
3
8
2
1
14
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

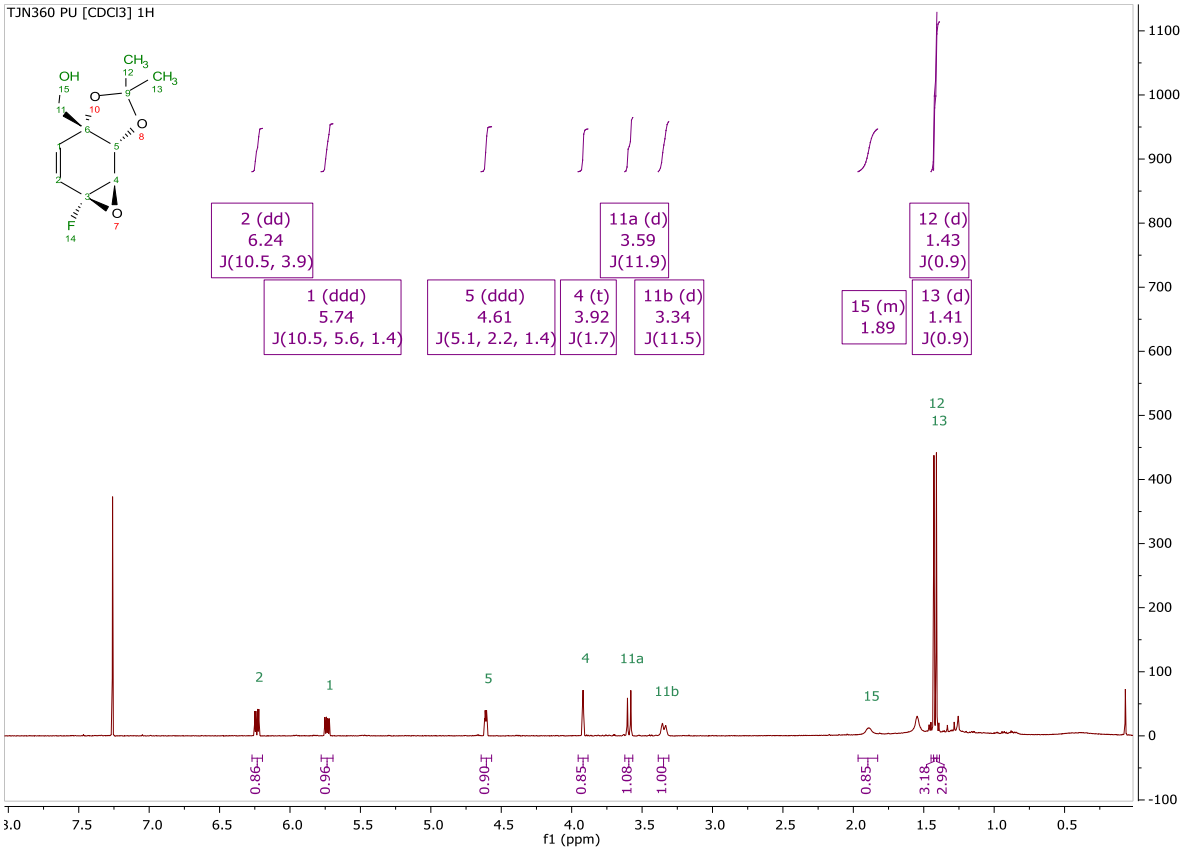
Sample-ID	tn_sel_TJN345A	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN345A_351625_93_01_57033.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	31/03/2017 10:36:07
Ionisation Mode	positive electrospray (ESI)		

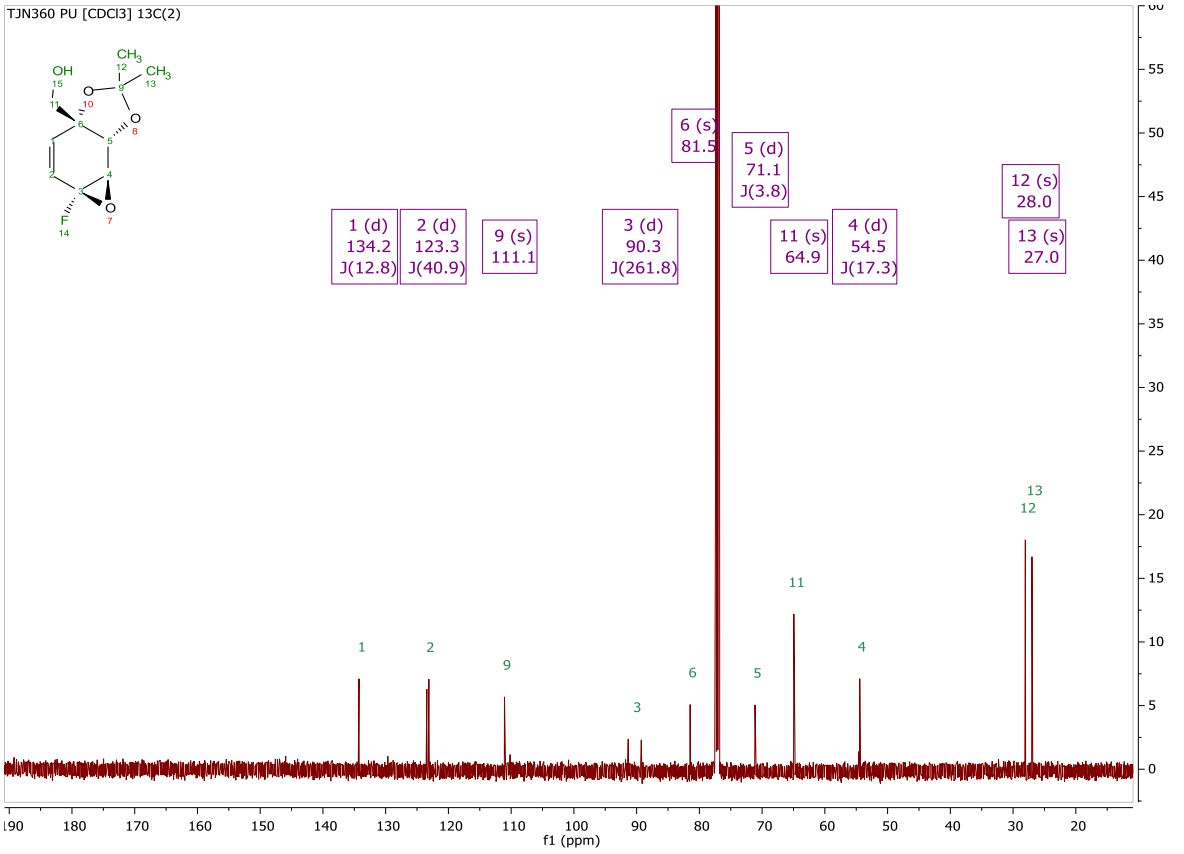
+MS, 1.0-1.3min #(60-77), -Spectral Bkgrnd

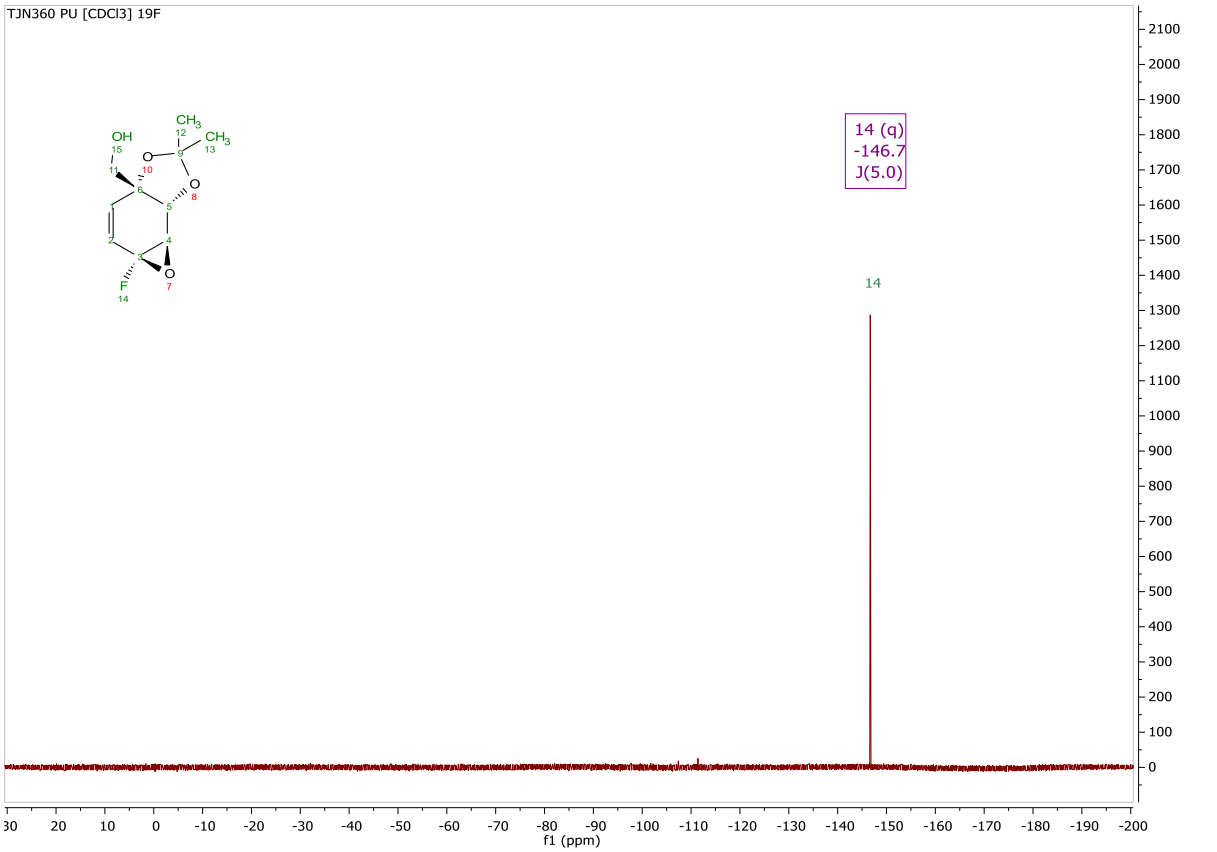


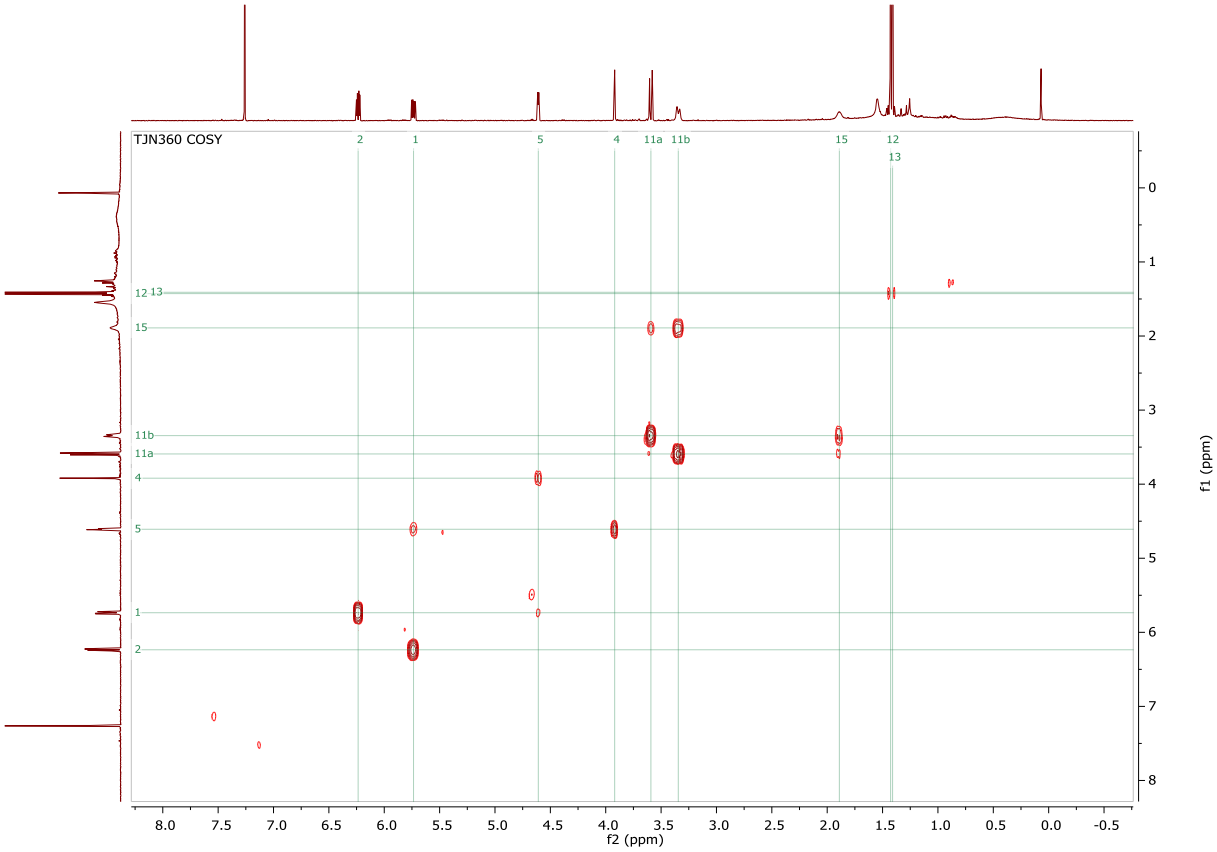
#	m/z	I	I %	Area	S/N
1	127.0155	1364	6.4	32	1261.5
2	132.1458	1475	7.0	22	1335.9
3	155.0134	1139	5.4	34	944.2
4	158.0288	745	3.5	14	610.7
5	214.1038	2039	9.6	36	891.4
6	236.0760	2024	9.6	58	521.6
7	267.0649	21153	100.0	1047	5092.9
8	268.0687	1618	7.6	90	395.1
9	393.3033	735	3.5	53	250.4
10	511.1391	1572	7.4	158	473.6

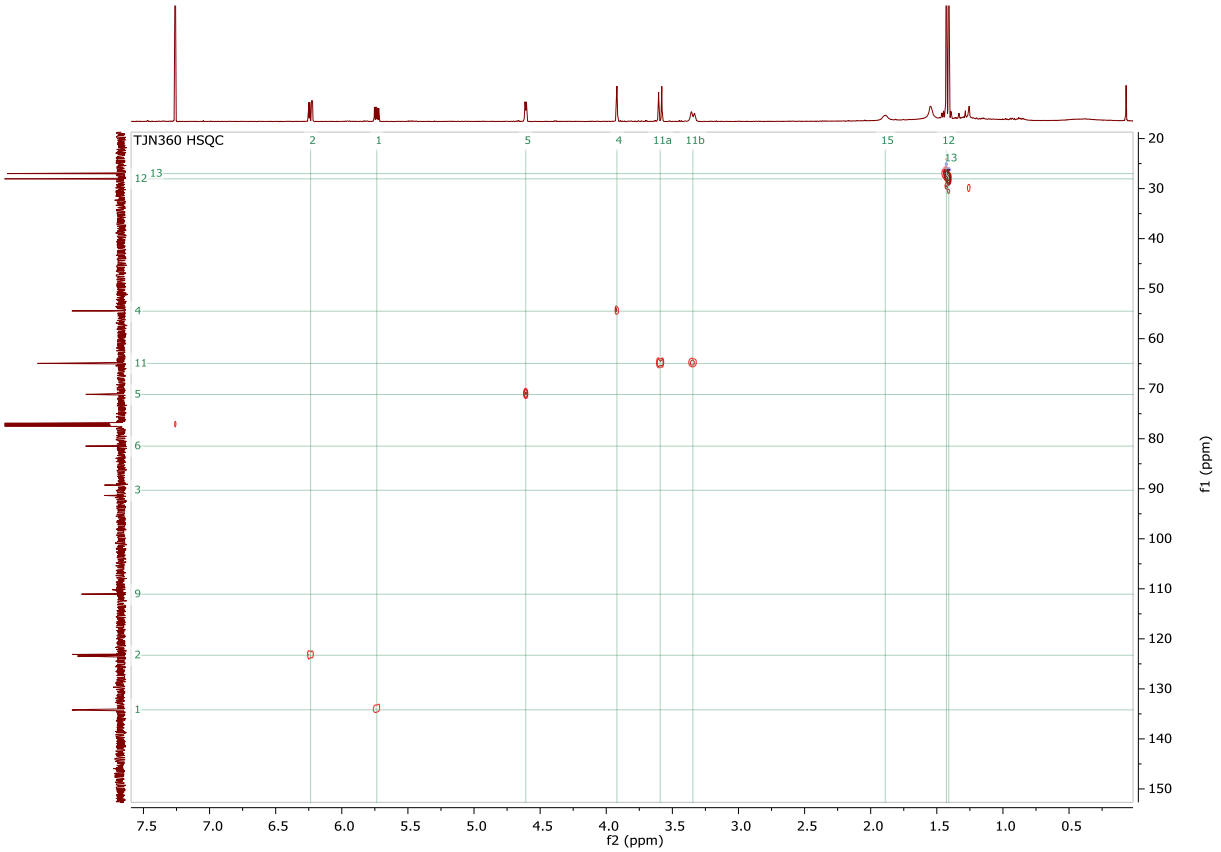
((3a*R*,5a*R*,6a*R*,6b*R*)-5a-Fluoro-2,2-dimethyl-6a,6b-dihydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxol-3a(5aH)-yl)methanol IV-40

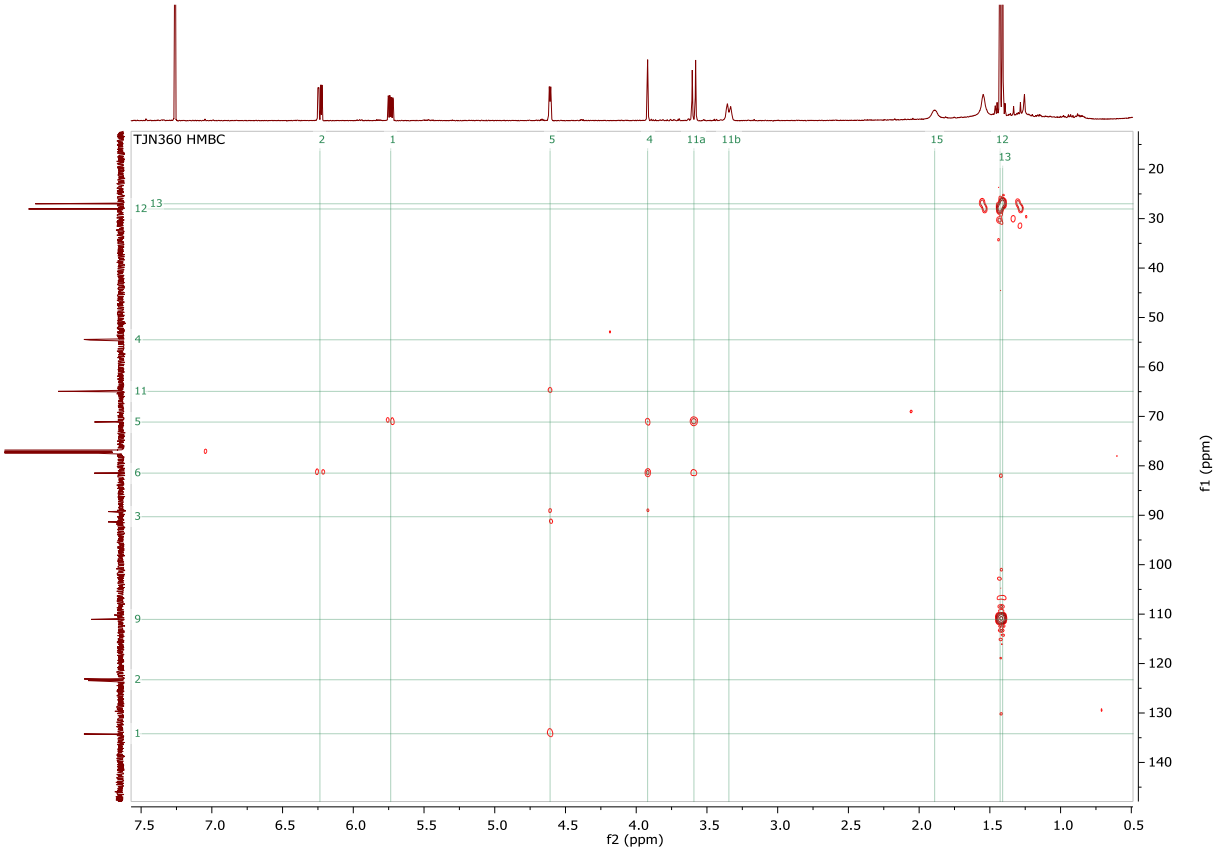





TJN360 PU [CDCl3] 19F
14 (q)
-146.7
J(5.0)
14
f1 (ppm)


TJN360 COSY
f2 (ppm)
f1 (ppm)

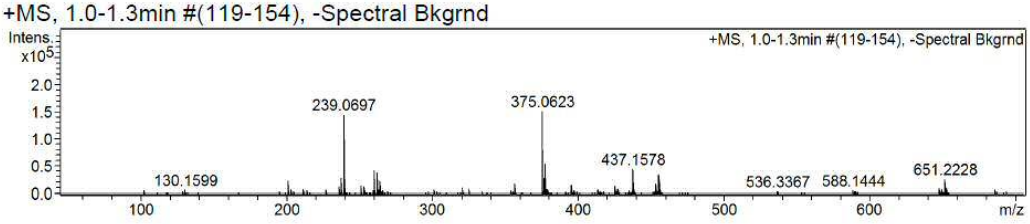

TJN360 HSQC
2
1
5
4
11a
11b
15
12
13
f2 (ppm)
f1 (ppm)


TJN360 HMBC
2
1
5
4
11a
11b
15
12
13
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

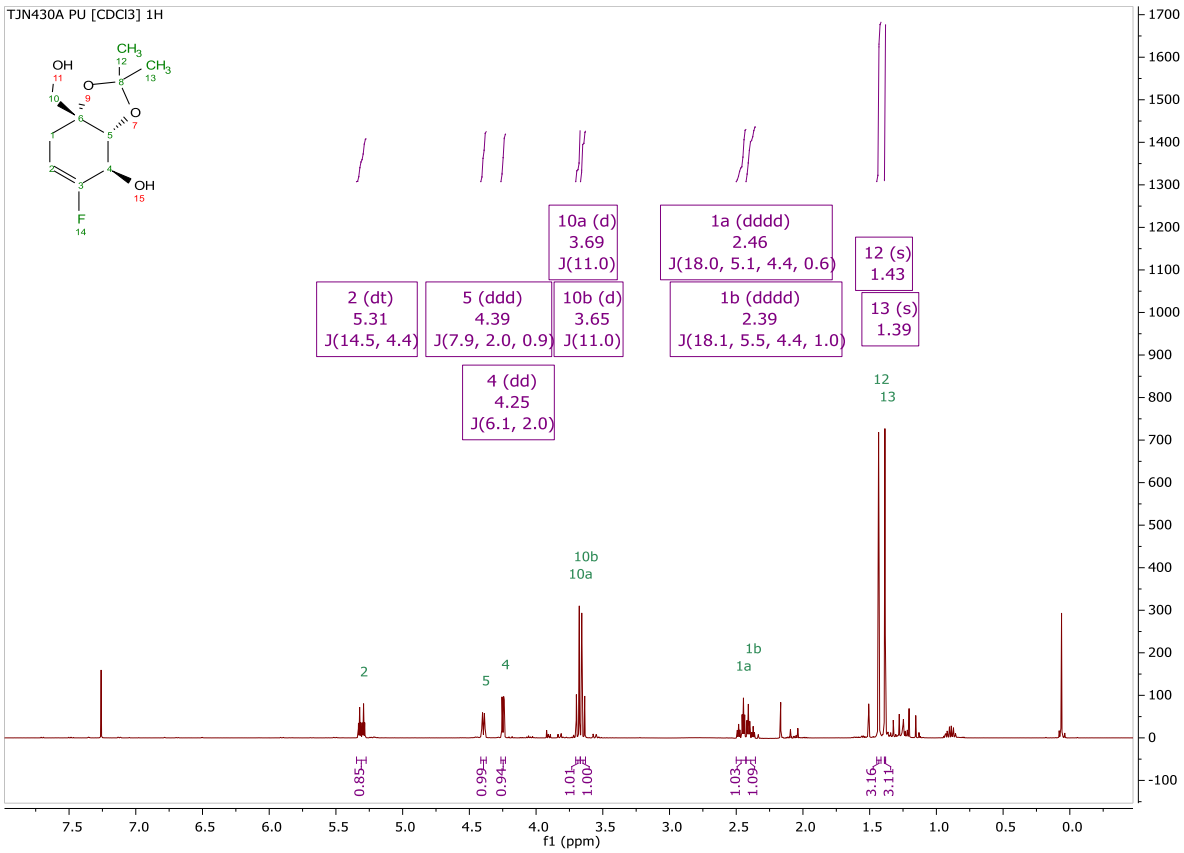
Sample-ID	tn_sel_TJN401	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN401_352682_16_01_58236.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	07/08/2017 10:50:15
Ionisation Mode	positive electrospray (ESI)		

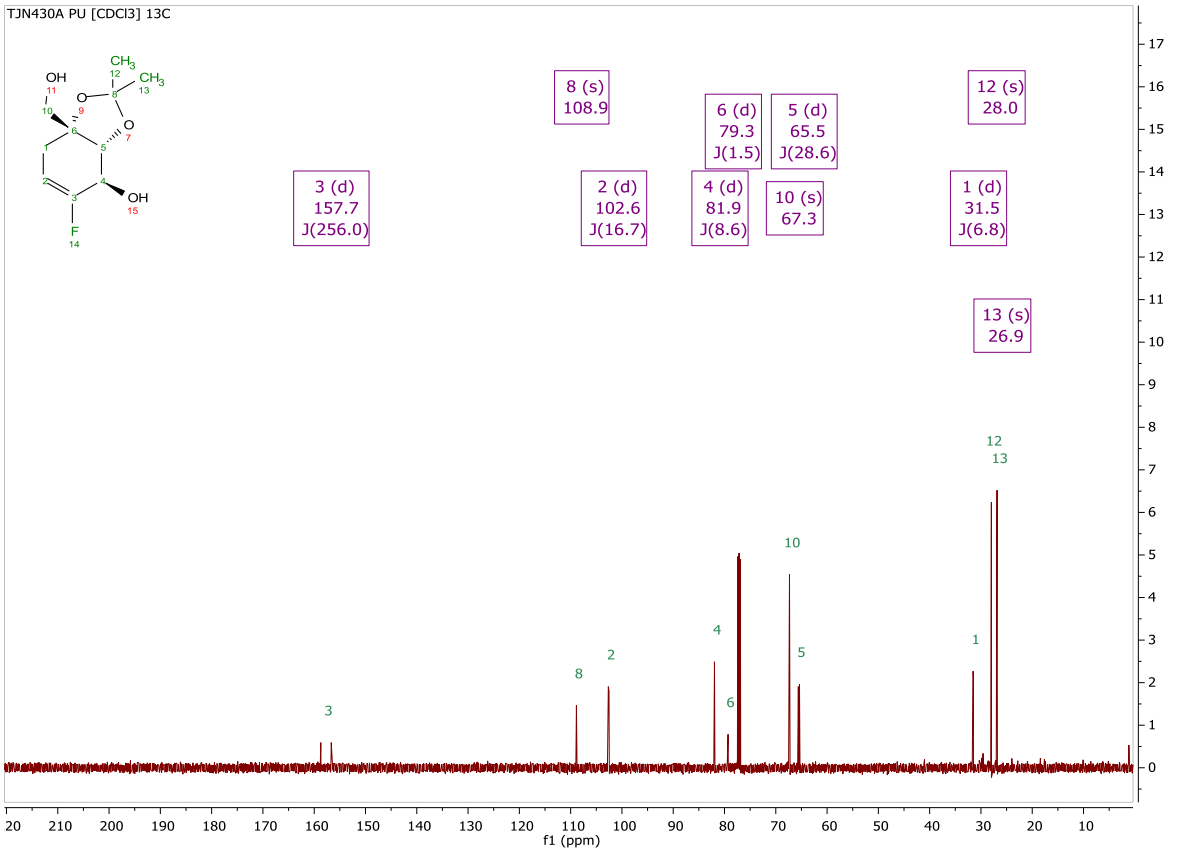
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

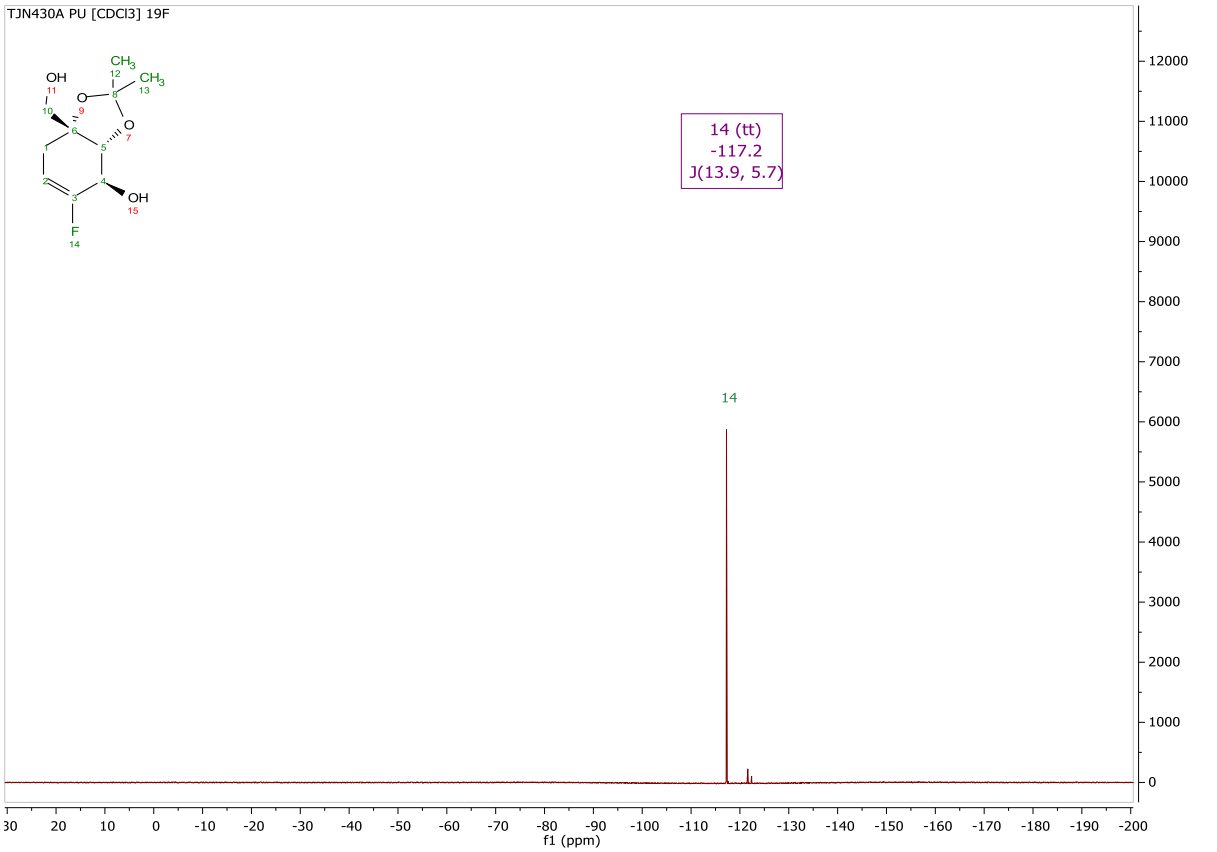


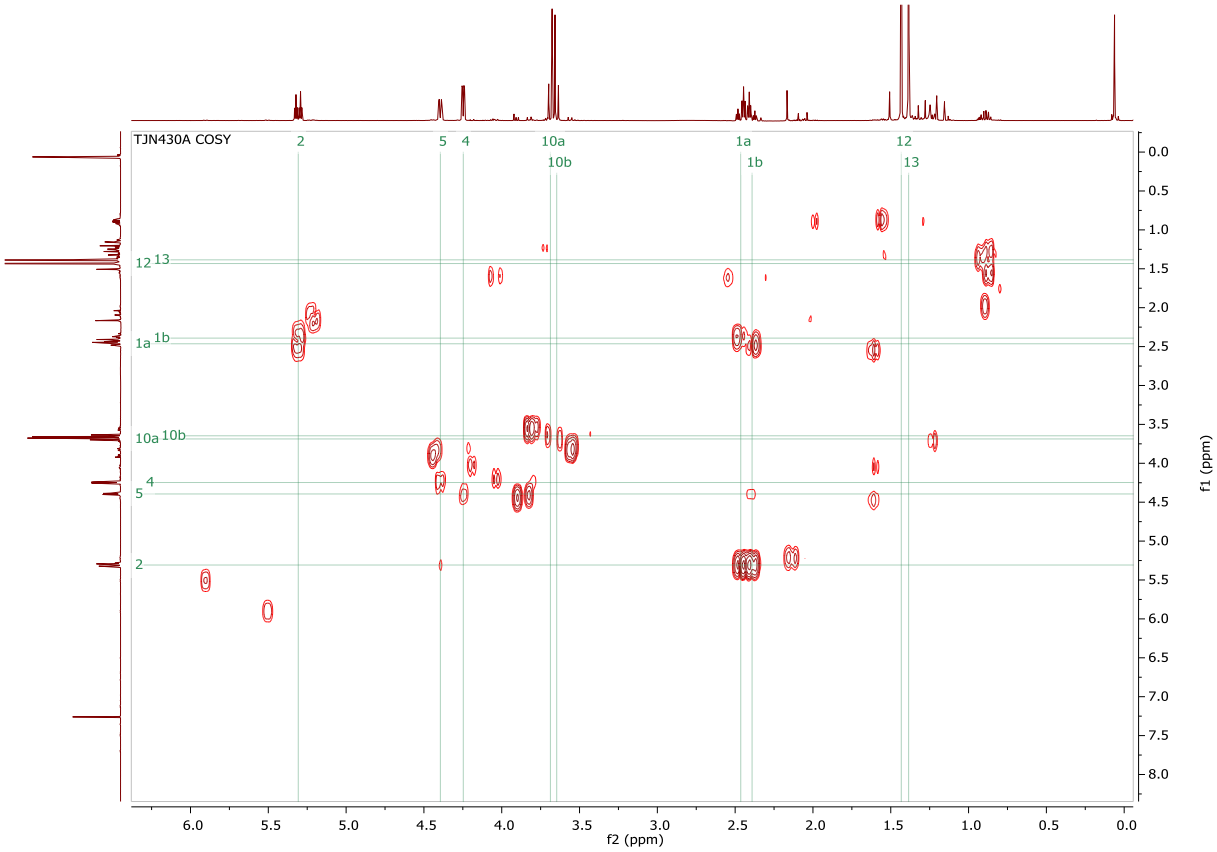
#	m/z	I	I %	Area	S/N
1	237.0793	28828	19.1	793	281.7
2	239.0697	145245	96.4	7028	1374.9
3	259.9451	41882	27.8	2255	446.4
4	261.9421	38181	25.3	2076	416.7
5	375.0623	150629	100.0	11181	1060.6
6	376.0650	28136	18.7	2008	198.2
7	377.0597	54799	36.4	4092	387.8
8	437.1578	44862	29.8	4013	425.2
9	455.1497	34937	23.2	3186	397.1
10	651.2228	26691	17.7	3573	618.3

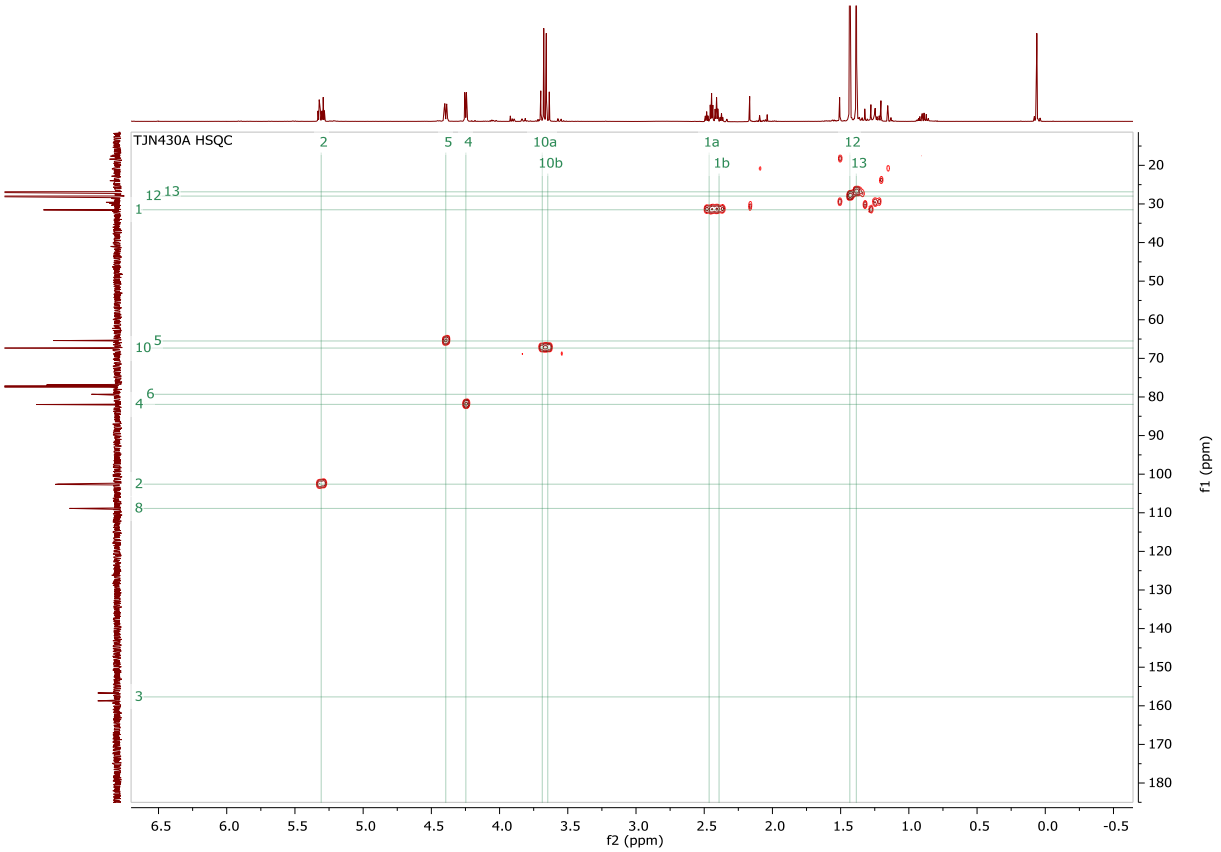
(3a*R*,4*R*,7a*R*)-5-Fluoro-7a-(hydroxymethyl)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol IV-41

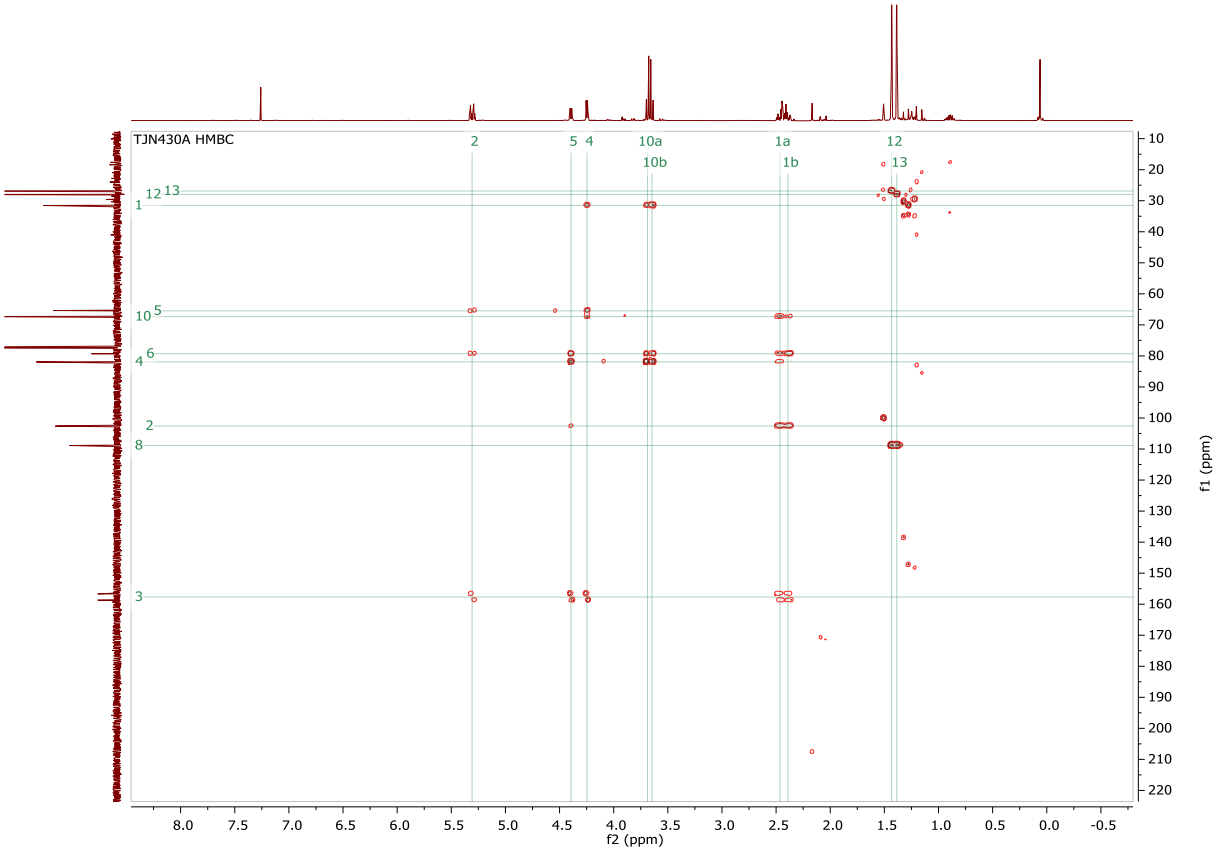





TJN430A PU [CDCl3] 19F
14 (tt)
-117.2
J(13.9, 5.7)
14
f1 (ppm)


TJN430A COSY
2
5
4
10a
10b
1a
1b
12
13
f2 (ppm)
f1 (ppm)

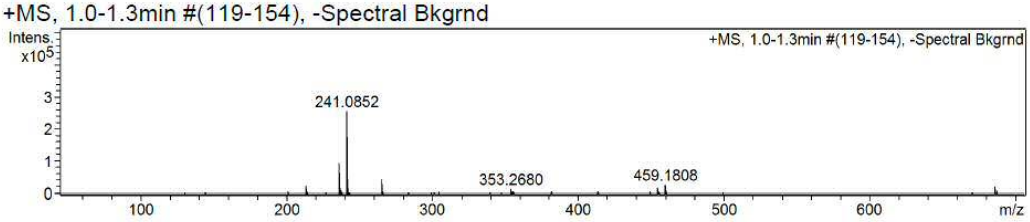

TJN430A HSQC
2
5
4
10a
10b
1a
1b
12
13
f2 (ppm)
f1 (ppm)


TJN430A HMBC
2
5
4
10a
10b
1a
1b
12
13
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

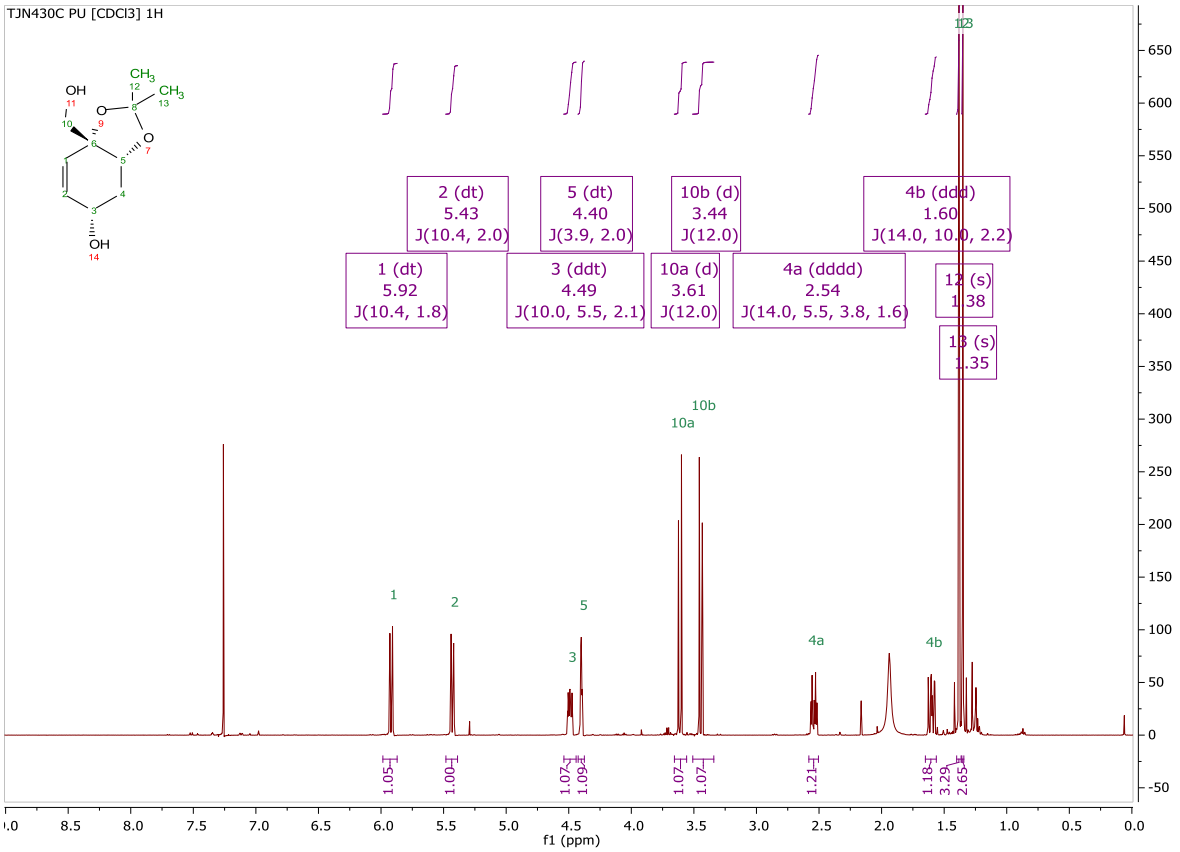
Sample-ID	tn_sel_TJN430A	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN430A_353704_65_01_59385.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	10/10/2017 11:42:41
Ionisation Mode	positive electrospray (ESI)		

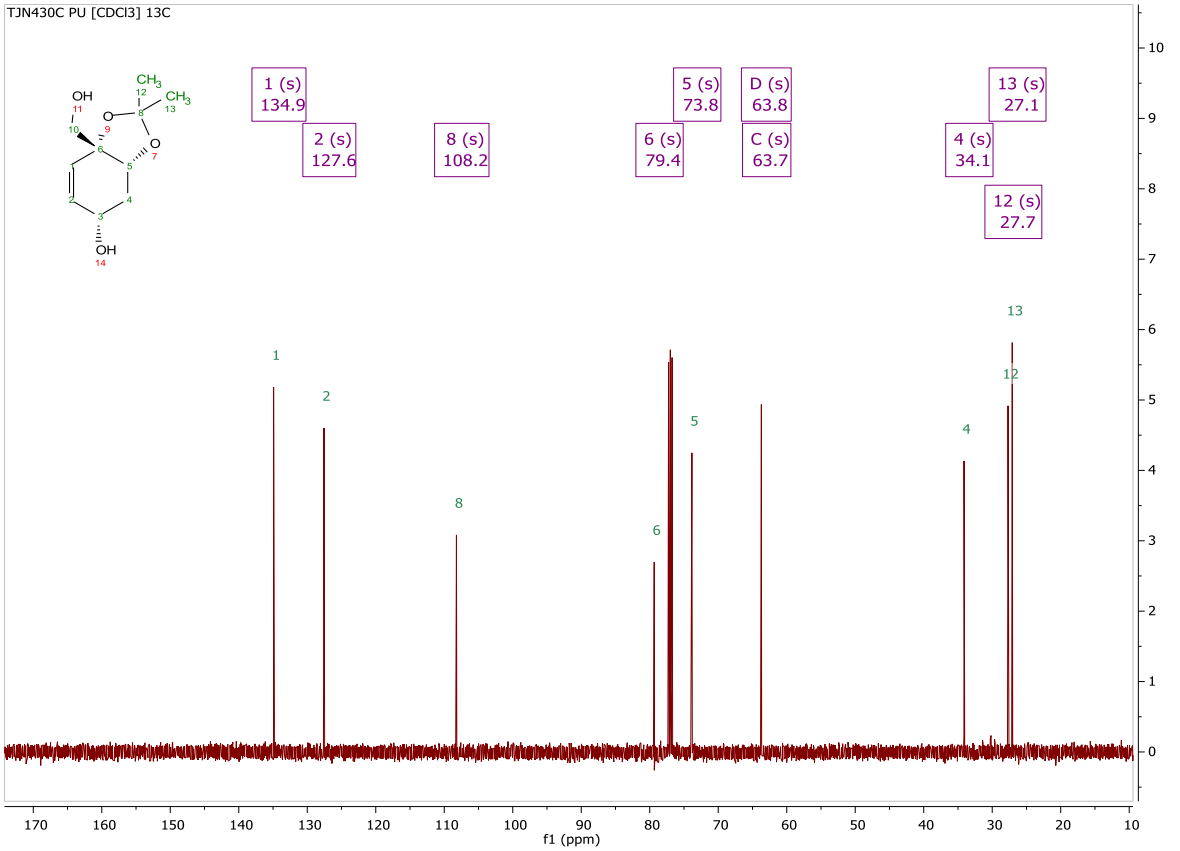
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

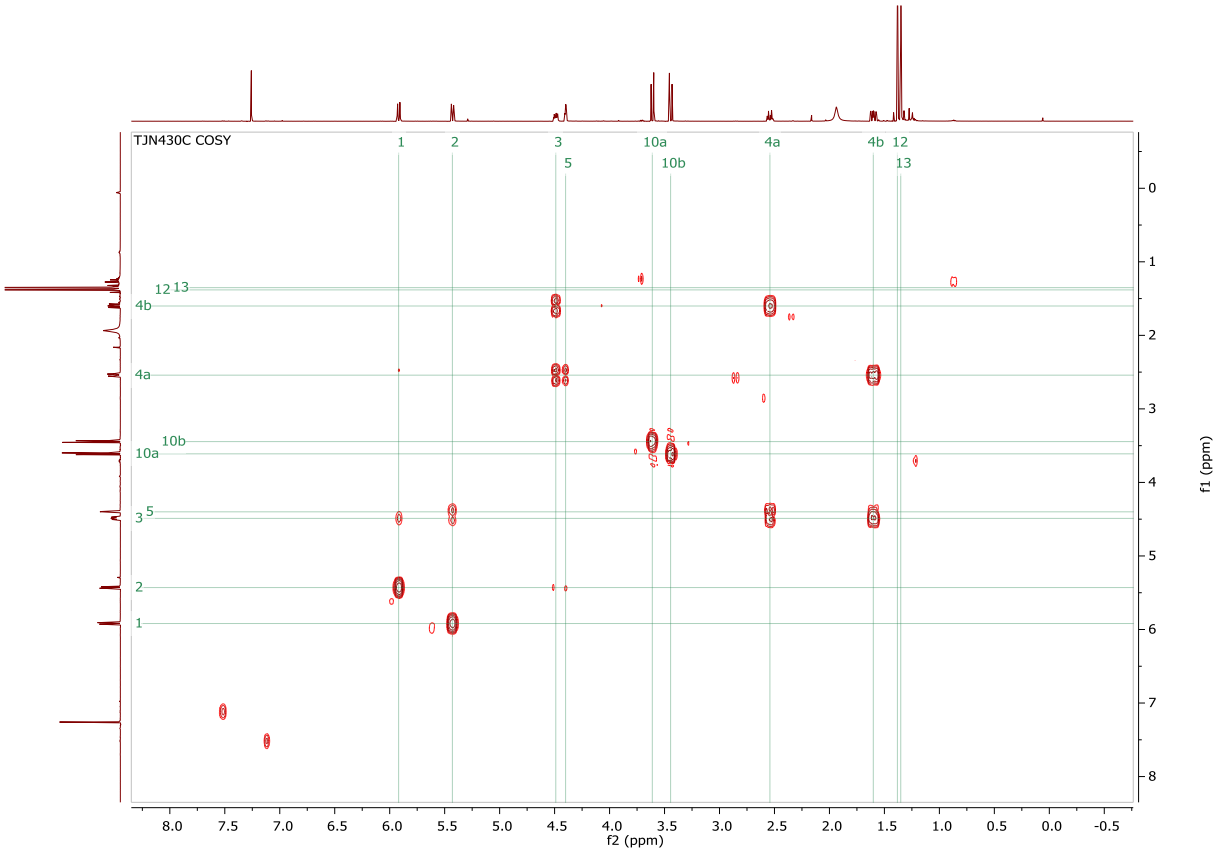


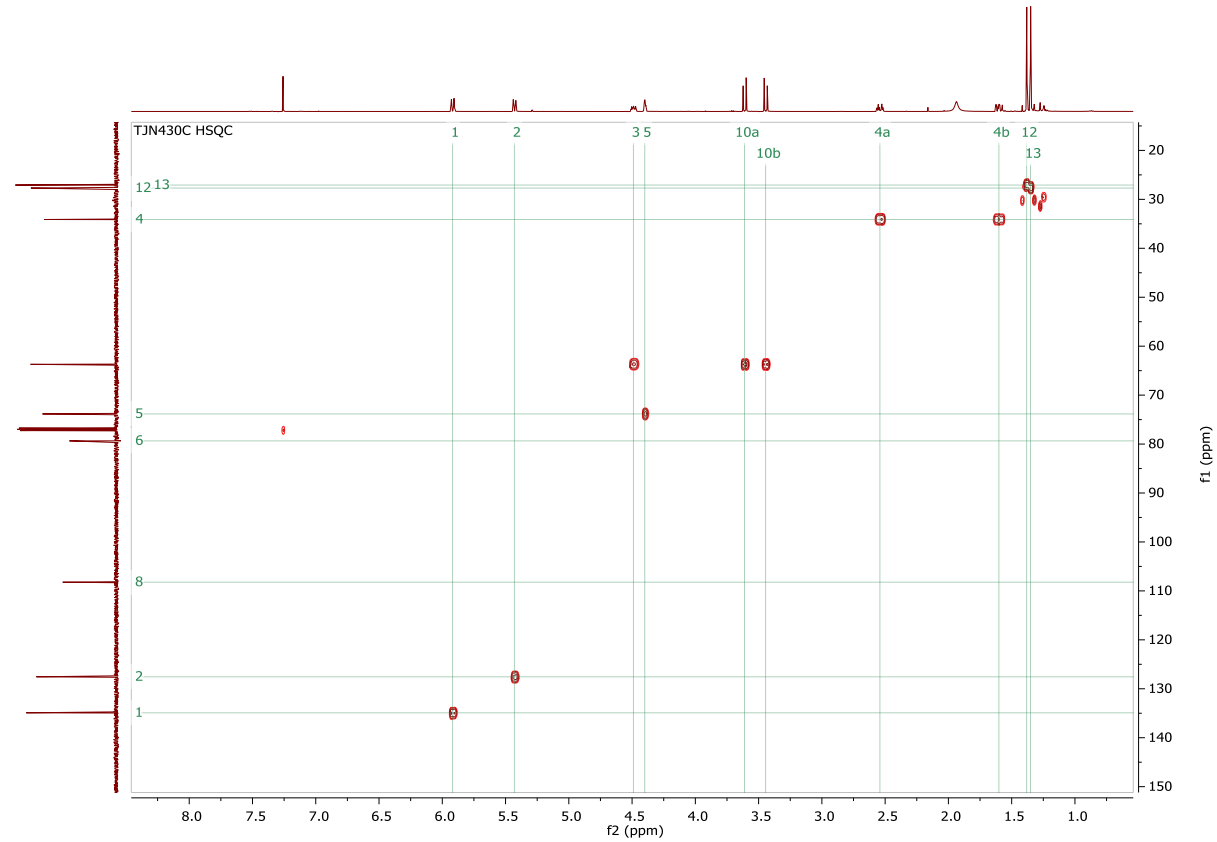
#	m/z	I	I %	Area	S/N
1	213.1460	23786	9.3	1047	856.4
2	236.0770	96204	37.7	1256	2043.0
3	237.0942	10750	4.2	134	224.2
4	241.0852	255209	100.0	12675	4974.0
5	242.0883	27908	10.9	1277	535.1
6	265.1045	45361	17.8	2348	907.1
7	353.2680	14799	5.8	949	528.8
8	454.1688	18748	7.3	1588	552.8
9	459.1808	27958	11.0	2507	785.1
10	685.4357	21700	8.5	3006	1751.9

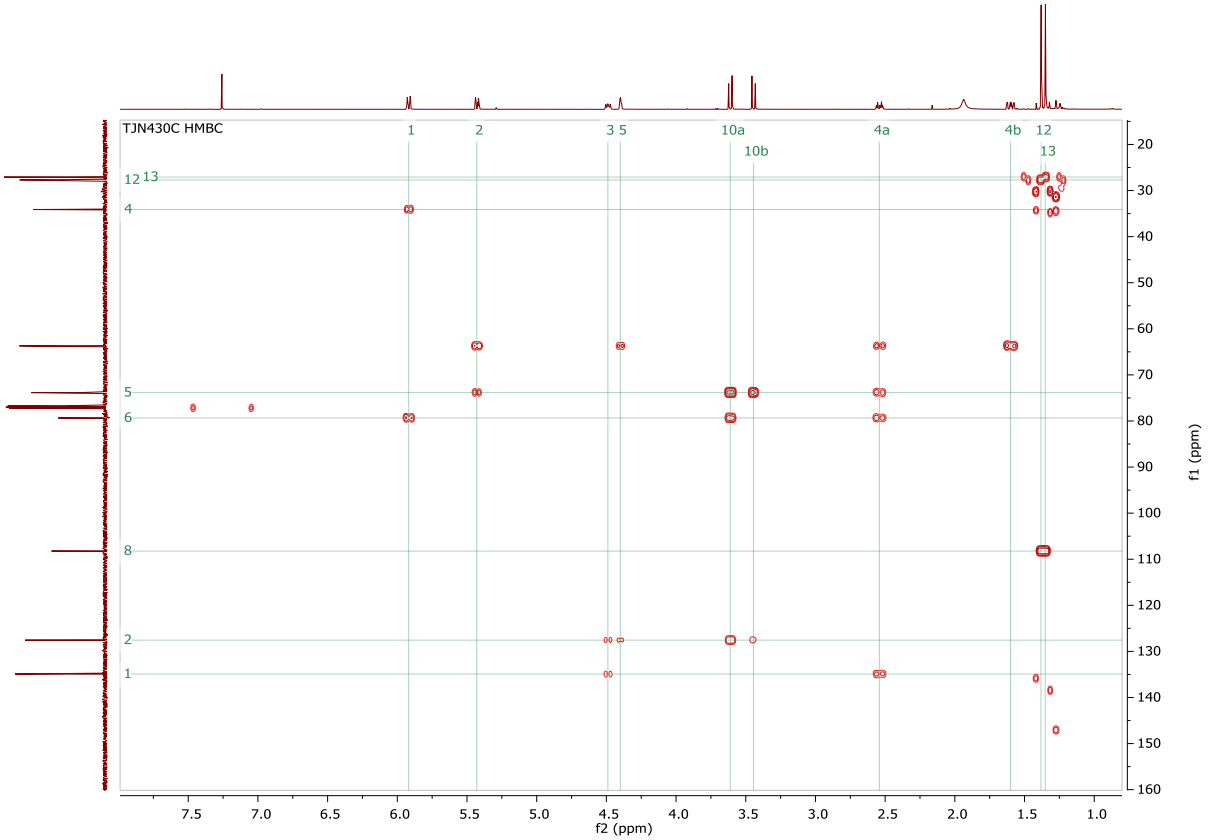
(3a*R*,5*S*,7a*R*)-7a-(Hydroxymethyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-ol IV-42






TJN430C COSY
1
2
3
5
10a
10b
4a
4b
12
13
f2 (ppm)
f1 (ppm)

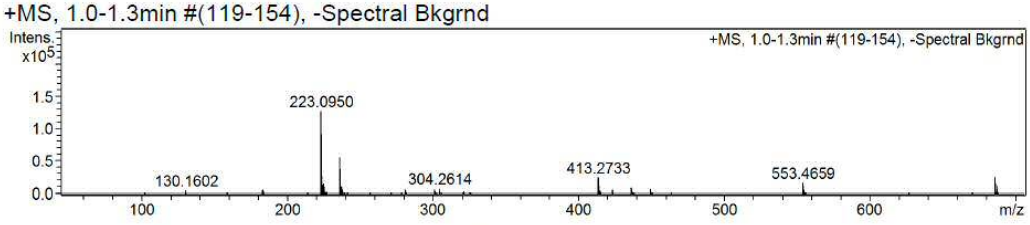

TJN430C HSQC
1
2
3 5
10a
10b
4a
4b
12
13
4
5
6
8
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

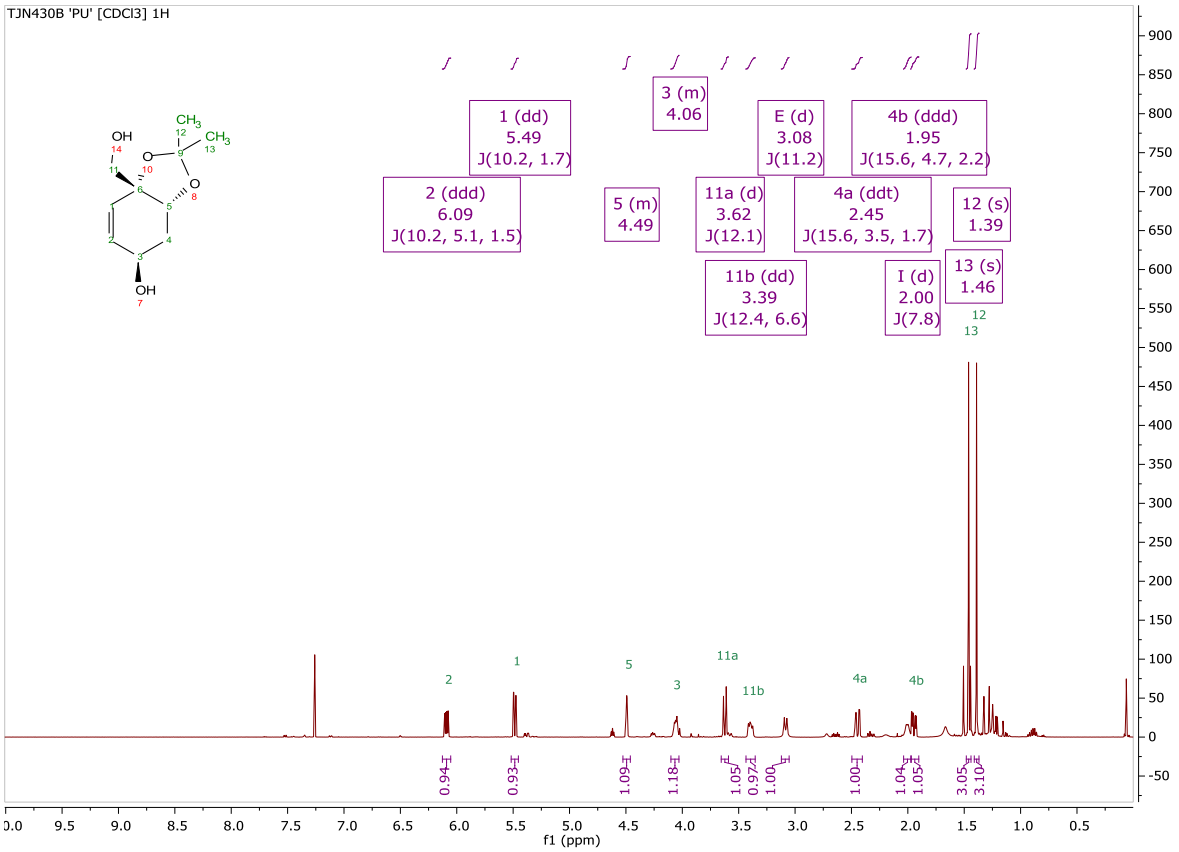
Sample-ID	tn_sel_TJN430C	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN430C_353706_67_01_59387.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	10/10/2017 11:49:39
Ionisation Mode	positive electrospray (ESI)		

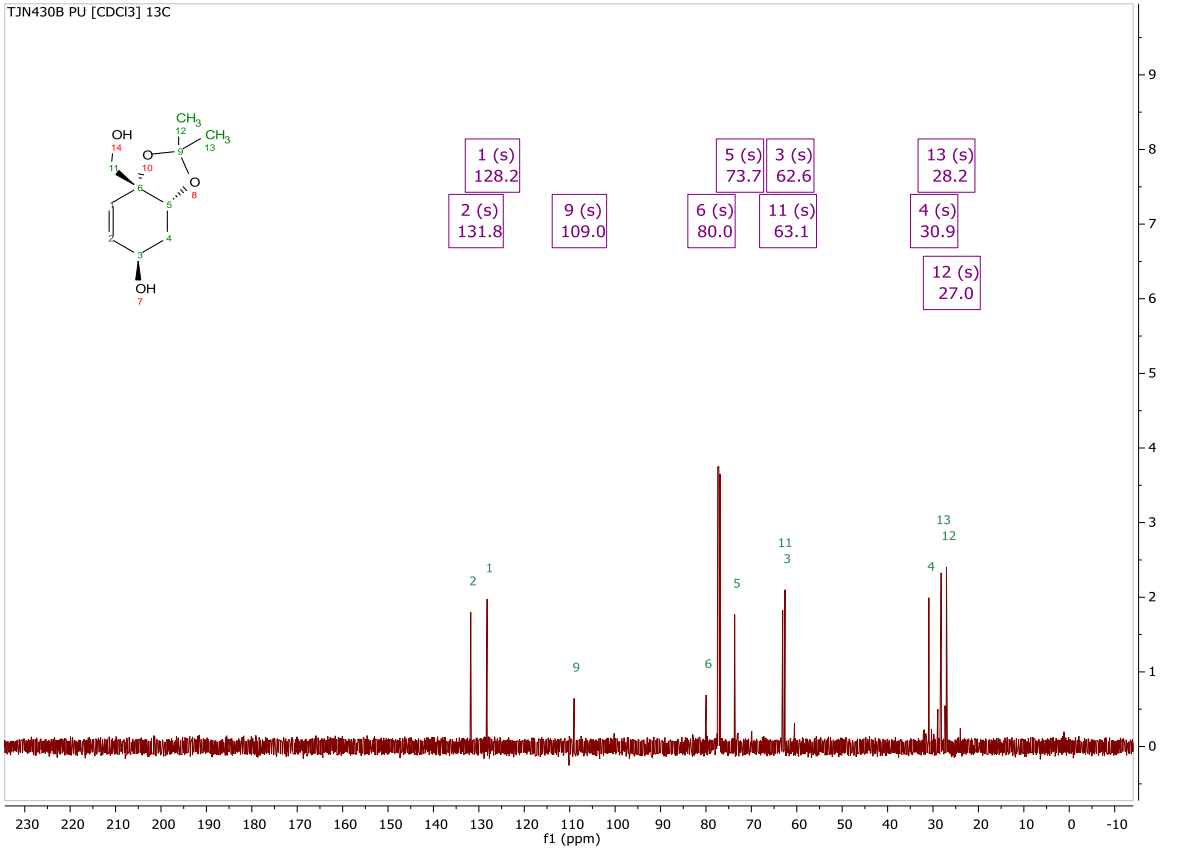
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

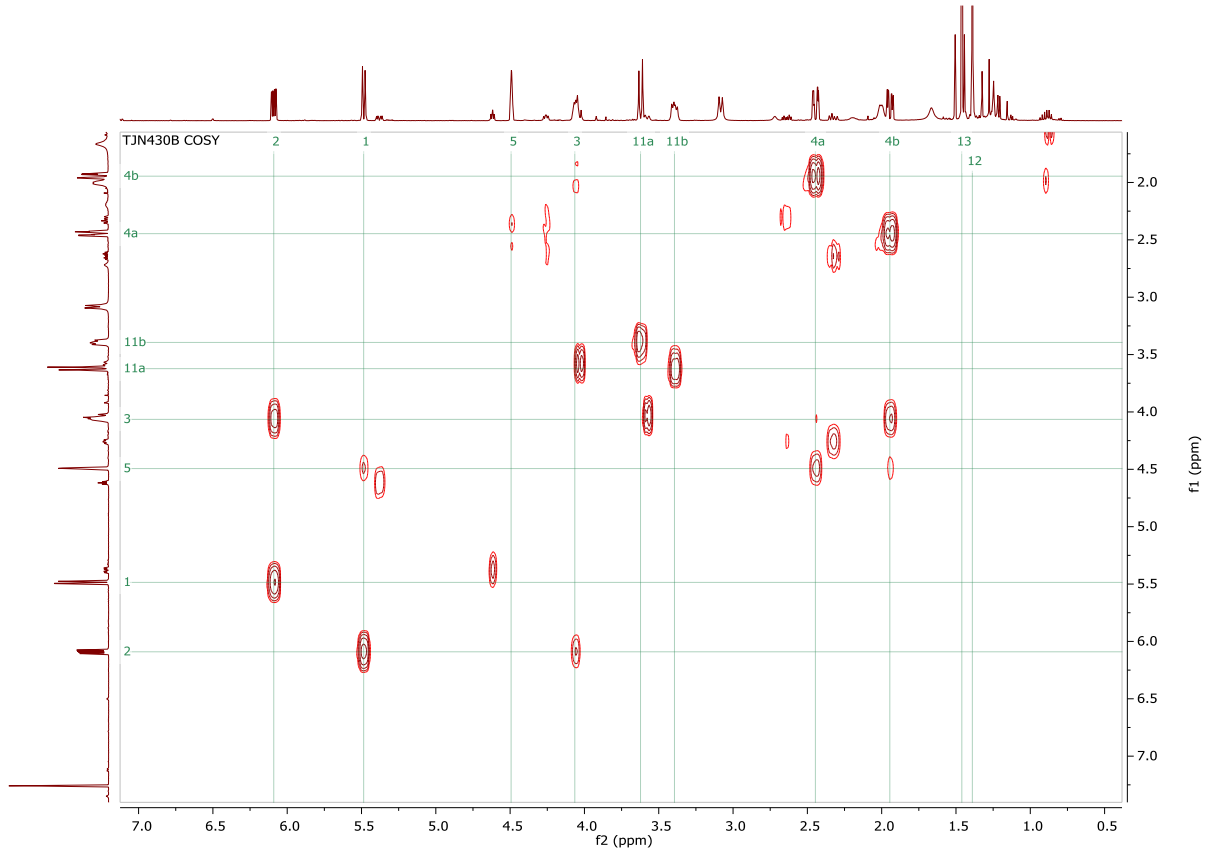


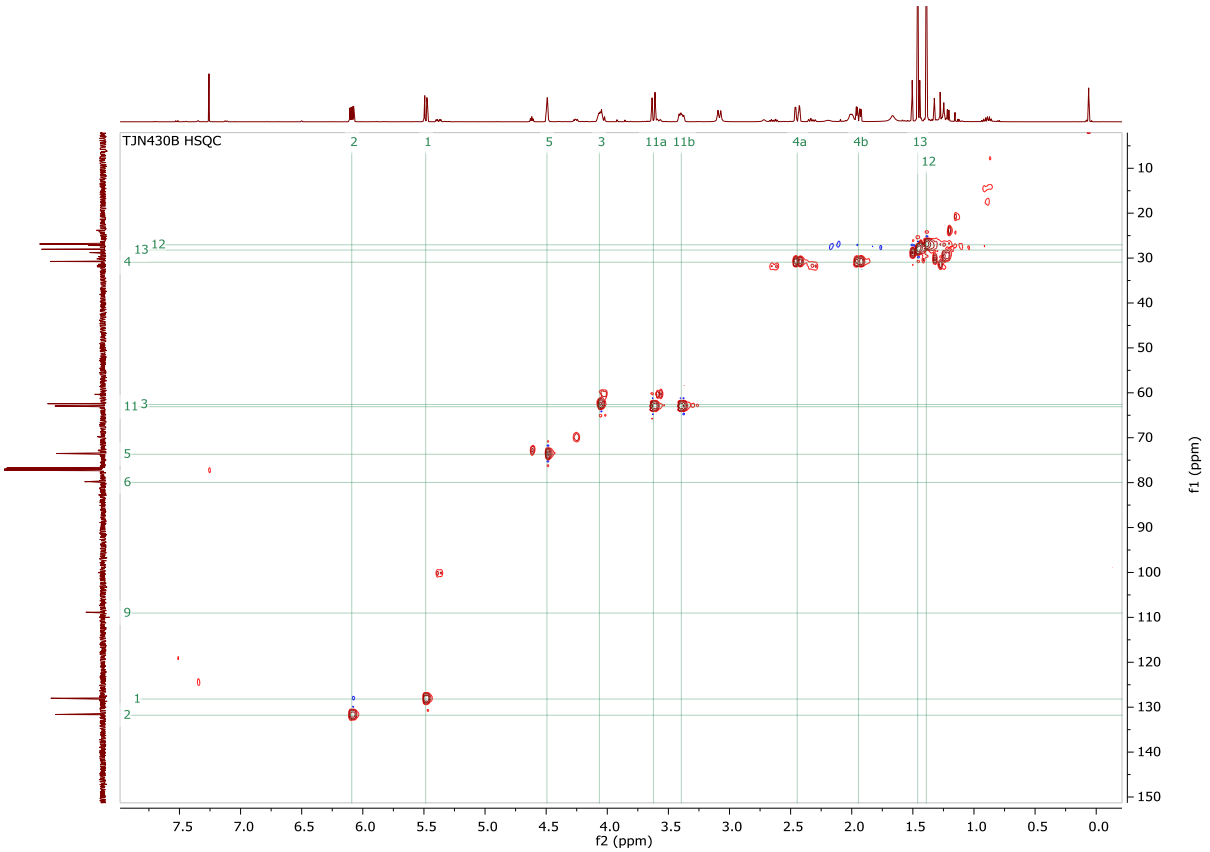
#	m/z	I	I %	Area	S/N
1	223.0950	126594	100.0	5426	5352.3
2	224.0980	13617	10.8	561	561.0
3	225.1100	14519	11.5	637	583.2
4	236.0949	55204	43.6	812	1743.2
5	237.0949	10386	8.2	132	321.7
6	413.2733	24672	19.5	1333	1097.6
7	436.1829	8791	6.9	534	411.8
8	553.4659	16744	13.2	1590	1119.4
9	685.4346	25659	20.3	3418	1575.8
10	686.4378	11900	9.4	1584	730.6

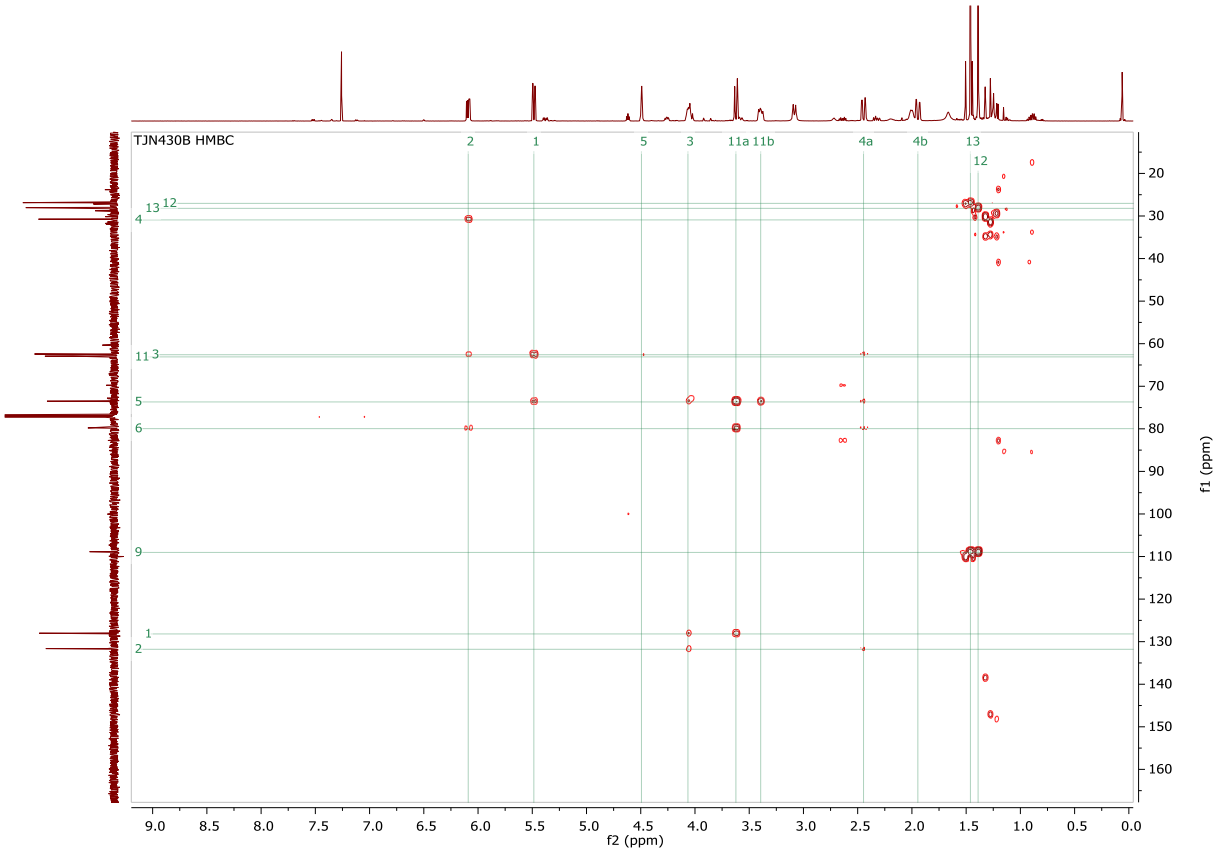
(3a*R*,5*S*,7a*R*)-7a-(Hydroxymethyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-5-ol IV-43






TJN430B COSY
2
1
5
3
11a
11b
4a
4b
13
12
4b
4a
11b
11a
3
5
1
2
f2 (ppm)
f1 (ppm)

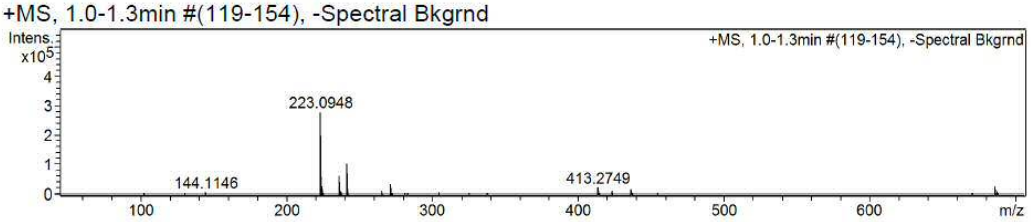

TJN430B HSQC
2
1
5
3
11a
11b
4a
4b
13
12
13 12
4
11 3
5
6
9
1
2
f2 (ppm)
f1 (ppm)



Confirmation of Expected Formula

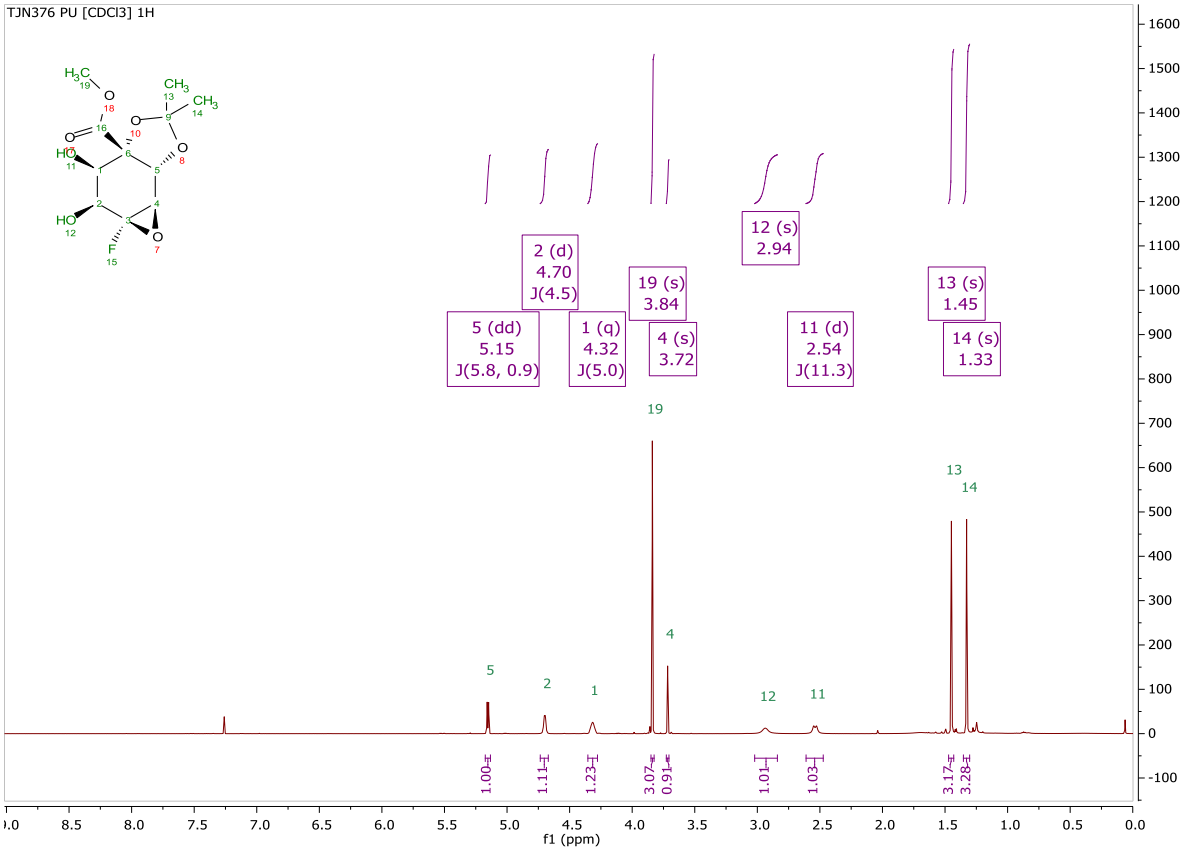
Sample-ID	tn_sel_TJN430B	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN430B_353705_66_01_59386.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	10/10/2017 11:46:09
Ionisation Mode	positive electrospray (ESI)		

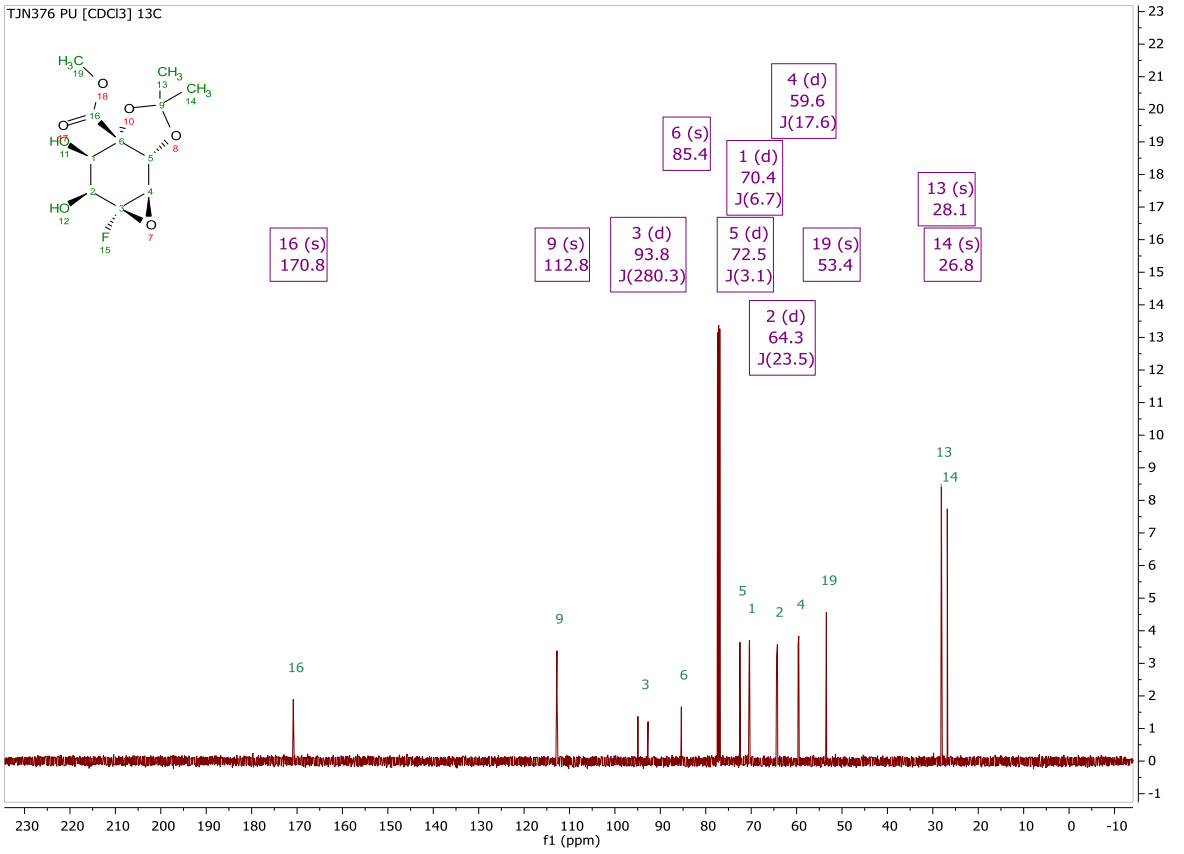
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

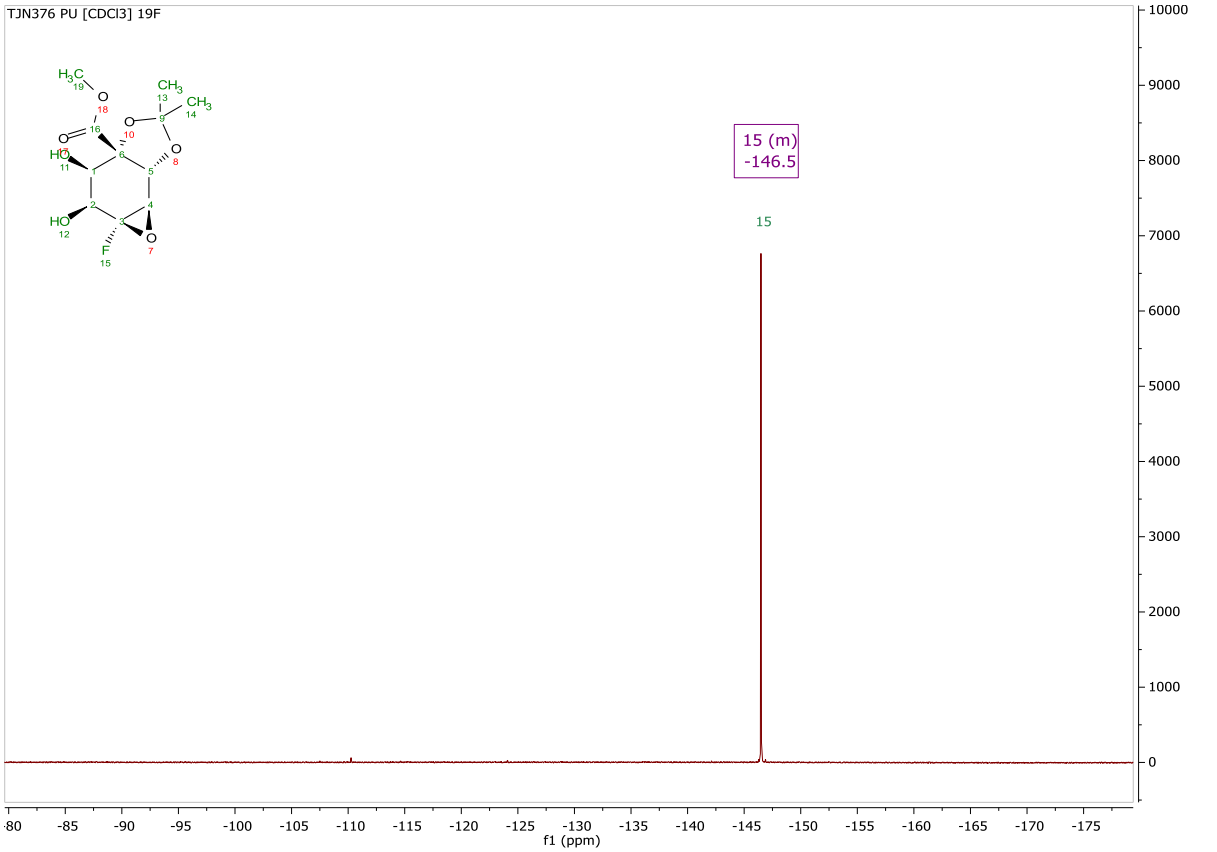


#	m/z	I	I %	Area	S/N
1	223.0948	278396	100.0	12446	8242.8
2	224.0981	28346	10.2	1221	817.2
3	236.0873	61292	22.0	844	1345.3
4	241.0865	102546	36.8	4668	2047.2
5	242.0889	11393	4.1	475	223.3
6	271.1878	34636	12.4	1855	791.7
7	413.2749	22930	8.2	1285	848.8
8	436.1837	16963	6.1	1155	659.1
9	685.4377	26379	9.5	3542	1522.0
10	686.4401	11771	4.2	1605	678.9

Methyl (3a*S*,4*R*,5*S*,5a*R*,6a*R*,6b*R*)-5a-fluoro-4,5-dihydroxy-2,2-dimethyltetrahydrooxireno[2',3':3,4]benzo[1,2-d][1,3]dioxole-3a(4H)-carboxylate IV-46



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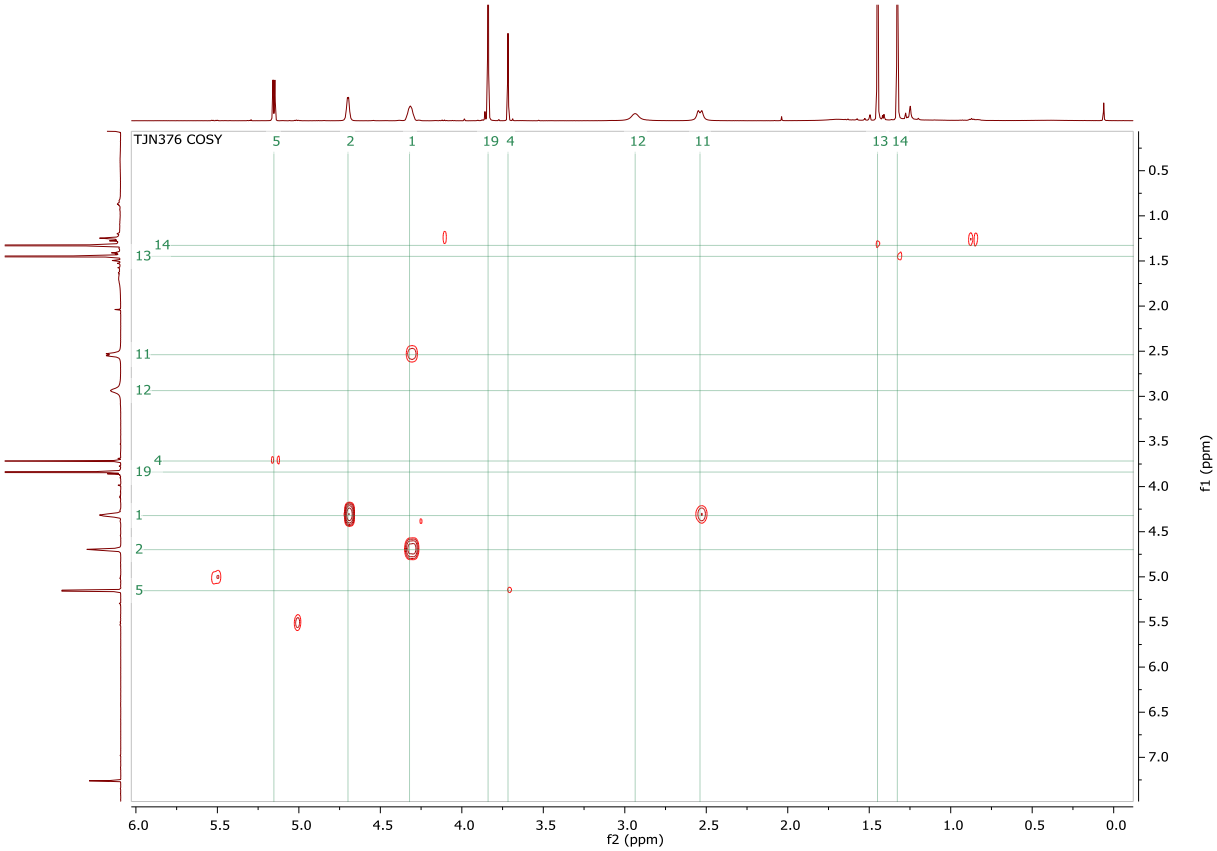
15
f1 (ppm)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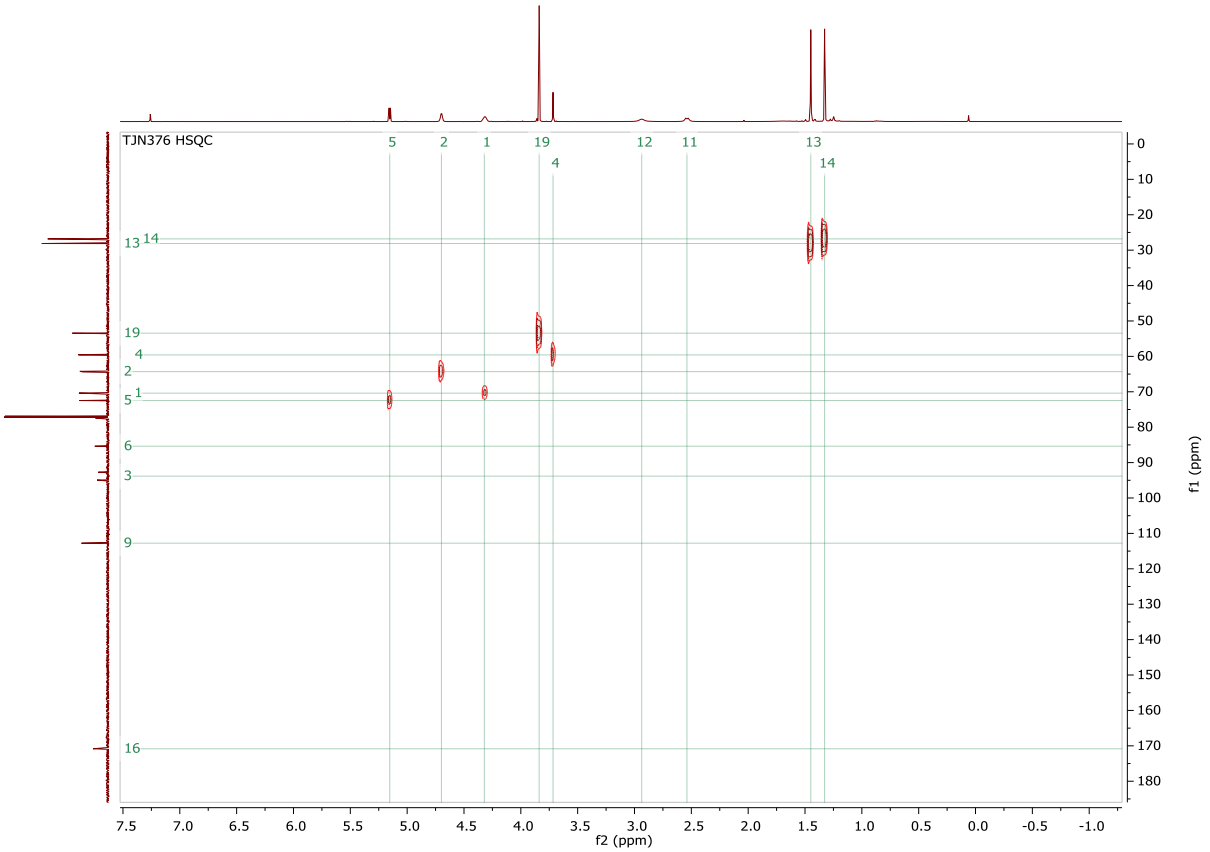
f2 (ppm)
f1 (ppm)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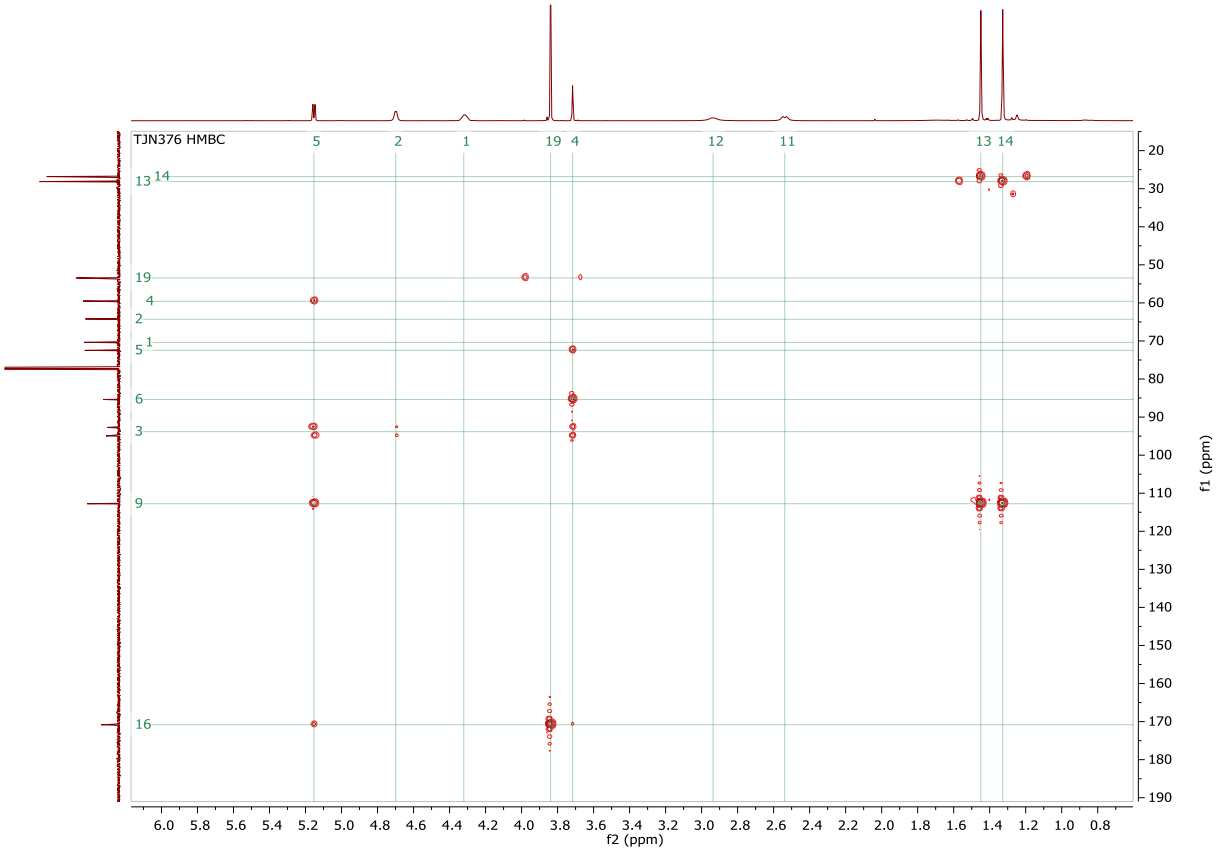
5
2
1
19
12
11
13
4
14
13 14
19
4
2
5 1
6
3
9
16
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180
f1 (ppm)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5
2
1
19 4
12
11
13 14
13 14
19
4
2
5 1
6
3
9
16
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f2 (ppm)
20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190
f1 (ppm)

Generic Display Report

Analysis Info

Analysis Name	D:\Data\Anneke\2017-06-21 Open Access\TJN376_RD7_01_13976.d	Acquisition Date	6/23/2017 2:51:20 PM
Method	sbr dan fia pos 75 -1000.m	Operator	BDAL@DE
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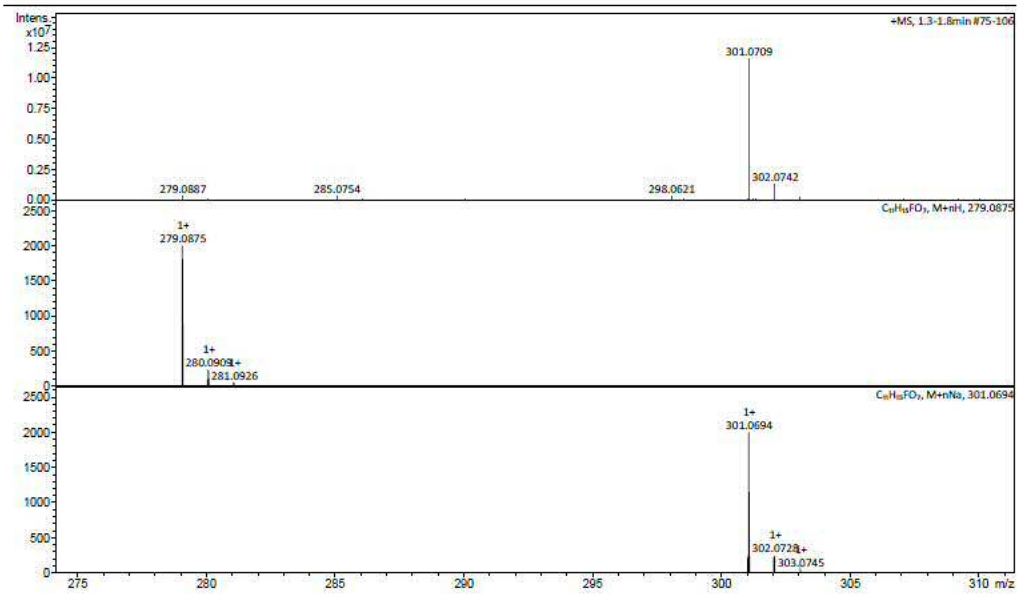
Comment			



Bruker Compass DataAnalysis 4.3 printed: 6/23/2017 3:24:33 PM by: BDAL@DE Page 1 of 1

Crystal structure data for IV-46

Table 1. Crystal data and structure refinement for s18sel11.

Identification code	s18sel11	
Empirical formula	C11 H15 F O7	
Formula weight	278.23	
Temperature	150.01(10) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 5.85700(10) Å	α= 90°.
	b = 11.24590(10) Å	β= 90°.
	c = 19.2255(2) Å	γ = 90°.
Volume	1266.33(3) $Å^3$	
Z	4	
Density (calculated)	1.459 Mg/m^3	
Absorption coefficient	1.145 mm^{-1}	
F(000)	584	
Crystal size	0.320 x 0.150 x 0.100 mm^3	
Theta range for data collection	4.555 to 72.989°.	
Index ranges	-6<=h<=7, -13<=k<=13, -23<=l<=23	
Reflections collected	12666	
Independent reflections	2529 [R(int) = 0.0299]	
Completeness to theta = 67.684°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.71709	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2529 / 0 / 183	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0258, wR2 = 0.0687	
R indices (all data)	R1 = 0.0266, wR2 = 0.0696	
Absolute structure parameter	0.03(6)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.224 and -0.173 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for s18sel11. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7247(2)	4958(1)	5643(1)	27(1)
O(2)	3528(2)	4947(1)	5364(1)	27(1)
O(3)	6864(2)	2652(1)	4795(1)	21(1)
O(4)	6380(2)	1722(1)	3508(1)	27(1)
O(5)	10542(2)	3266(1)	3829(1)	24(1)
O(6)	8344(2)	6348(1)	4113(1)	26(1)
O(7)	4950(2)	5365(1)	3973(1)	21(1)
F	9300(2)	3186(1)	2691(1)	32(1)
C(1)	6640(4)	5056(2)	6373(1)	37(1)
C(2)	5510(3)	4905(1)	5202(1)	20(1)
C(3)	6286(2)	4693(1)	4446(1)	18(1)
C(4)	5755(2)	3380(1)	4295(1)	18(1)
C(5)	6434(3)	2976(1)	3561(1)	20(1)
C(6)	8739(3)	3452(2)	3363(1)	22(1)
C(7)	9793(3)	4496(2)	3679(1)	22(1)
C(8)	8715(3)	5132(1)	4286(1)	20(1)
C(9)	6053(3)	6496(2)	3863(1)	24(1)
C(10)	6043(4)	6734(2)	3090(1)	41(1)
C(11)	4909(4)	7454(2)	4288(1)	37(1)

Table 3. Bond lengths [Å] for s18sel11.

O(1)-C(2)	1.326(2)
O(1)-C(1)	1.4512(19)
O(2)-C(2)	1.203(2)
O(3)-C(4)	1.4207(18)
O(3)-H(3)	0.85(3)
O(4)-C(5)	1.415(2)
O(4)-H(4)	0.81(3)
O(5)-C(6)	1.4009(19)
O(5)-C(7)	1.479(2)
O(6)-C(8)	1.4243(19)
O(6)-C(9)	1.435(2)
O(7)-C(3)	1.4170(18)
O(7)-C(9)	1.4421(19)
F-C(6)	1.3654(18)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(3)	1.542(2)
C(3)-C(4)	1.537(2)
C(3)-C(8)	1.537(2)
C(4)-C(5)	1.533(2)
C(4)-H(4A)	1.0000
C(5)-C(6)	1.501(2)
C(5)-H(5)	1.0000
C(6)-C(7)	1.459(2)
C(7)-C(8)	1.507(2)
C(7)-H(7)	1.0000
C(8)-H(8)	1.0000
C(9)-C(11)	1.509(2)
C(9)-C(10)	1.511(2)
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800

Table 4. Bond angles [°] for s18sel11.

C(2)-O(1)-C(1)	115.67(14)
C(4)-O(3)-H(3)	106.3(18)
C(5)-O(4)-H(4)	108.5(17)
C(6)-O(5)-C(7)	60.79(10)
C(8)-O(6)-C(9)	109.36(12)
C(3)-O(7)-C(9)	108.49(12)
O(1)-C(1)-H(1A)	109.5
O(1)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(1)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(2)-C(2)-O(1)	124.98(15)
O(2)-C(2)-C(3)	122.32(14)
O(1)-C(2)-C(3)	112.58(13)
O(7)-C(3)-C(4)	106.27(11)
O(7)-C(3)-C(8)	102.22(12)
C(4)-C(3)-C(8)	117.27(13)
O(7)-C(3)-C(2)	111.04(12)
C(4)-C(3)-C(2)	105.49(12)
C(8)-C(3)-C(2)	114.30(12)
O(3)-C(4)-C(5)	109.50(12)
O(3)-C(4)-C(3)	109.48(12)
C(5)-C(4)-C(3)	113.92(12)
O(3)-C(4)-H(4A)	107.9
C(5)-C(4)-H(4A)	107.9
C(3)-C(4)-H(4A)	107.9
O(4)-C(5)-C(6)	110.91(13)
O(4)-C(5)-C(4)	110.88(13)
C(6)-C(5)-C(4)	111.18(13)
O(4)-C(5)-H(5)	107.9
C(6)-C(5)-H(5)	107.9
C(4)-C(5)-H(5)	107.9
F-C(6)-O(5)	112.97(13)
F-C(6)-C(7)	117.95(14)
O(5)-C(6)-C(7)	62.25(10)
F-C(6)-C(5)	112.27(14)

O(5)-C(6)-C(5)	117.52(13)
C(7)-C(6)-C(5)	124.13(14)
C(6)-C(7)-O(5)	56.95(10)
C(6)-C(7)-C(8)	121.83(14)
O(5)-C(7)-C(8)	114.70(12)
C(6)-C(7)-H(7)	116.5
O(5)-C(7)-H(7)	116.5
C(8)-C(7)-H(7)	116.5
O(6)-C(8)-C(7)	109.87(12)
O(6)-C(8)-C(3)	102.36(12)
C(7)-C(8)-C(3)	112.95(13)
O(6)-C(8)-H(8)	110.5
C(7)-C(8)-H(8)	110.5
C(3)-C(8)-H(8)	110.5
O(6)-C(9)-O(7)	105.53(12)
O(6)-C(9)-C(11)	108.47(14)
O(7)-C(9)-C(11)	110.58(14)
O(6)-C(9)-C(10)	110.73(15)
O(7)-C(9)-C(10)	107.38(14)
C(11)-C(9)-C(10)	113.84(17)
C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(9)-C(11)-H(11A)	109.5
C(9)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(9)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5

Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for s18sel11. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	28(1)	39(1)	15(1)	-2(1)	-1(1)	-4(1)
O(2)	24(1)	33(1)	25(1)	-1(1)	5(1)	1(1)
O(3)	23(1)	24(1)	17(1)	5(1)	-1(1)	1(1)
O(4)	33(1)	24(1)	23(1)	-4(1)	-5(1)	1(1)
O(5)	17(1)	31(1)	25(1)	1(1)	-2(1)	4(1)
O(6)	24(1)	22(1)	32(1)	3(1)	-4(1)	-4(1)
O(7)	19(1)	22(1)	21(1)	3(1)	-4(1)	1(1)
F	34(1)	44(1)	18(1)	-4(1)	6(1)	2(1)
C(1)	44(1)	53(1)	15(1)	-5(1)	1(1)	-9(1)
C(2)	24(1)	16(1)	19(1)	1(1)	0(1)	-1(1)
C(3)	16(1)	22(1)	15(1)	1(1)	-2(1)	1(1)
C(4)	15(1)	21(1)	17(1)	2(1)	-1(1)	1(1)
C(5)	19(1)	24(1)	17(1)	-2(1)	-3(1)	2(1)
C(6)	21(1)	30(1)	16(1)	1(1)	1(1)	4(1)
C(7)	15(1)	30(1)	21(1)	4(1)	-1(1)	0(1)
C(8)	17(1)	24(1)	19(1)	2(1)	-2(1)	-2(1)
C(9)	25(1)	22(1)	24(1)	4(1)	-2(1)	-1(1)
C(10)	48(1)	50(1)	26(1)	15(1)	-7(1)	-10(1)
C(11)	38(1)	23(1)	51(1)	-4(1)	2(1)	3(1)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for s18sel11.

	x	y	z	U(eq)
H(3)	5820(50)	2390(30)	5062(15)	42(7)
H(4)	6790(50)	1440(20)	3875(14)	39(7)
H(1A)	5682	5761	6442	56
H(1B)	8031	5130	6653	56
H(1C)	5797	4344	6516	56
H(4A)	4072	3262	4346	21
H(5)	5289	3306	3227	24
H(7)	10814	4981	3374	26
H(8)	9704	5065	4708	24
H(10A)	6825	6084	2848	62
H(10B)	6833	7484	2995	62
H(10C)	4463	6787	2925	62
H(11A)	5699	8212	4214	56
H(11B)	4972	7242	4782	56
H(11C)	3311	7531	4143	56

Table 7. Torsion angles [°] for s18sel11.

C(1)-O(1)-C(2)-O(2)	1.0(2)
C(1)-O(1)-C(2)-C(3)	-175.02(14)
C(9)-O(7)-C(3)-C(4)	-154.46(12)
C(9)-O(7)-C(3)-C(8)	-30.99(15)
C(9)-O(7)-C(3)-C(2)	91.32(14)
O(2)-C(2)-C(3)-O(7)	42.7(2)
O(1)-C(2)-C(3)-O(7)	-141.18(13)
O(2)-C(2)-C(3)-C(4)	-72.06(18)
O(1)-C(2)-C(3)-C(4)	104.11(14)
O(2)-C(2)-C(3)-C(8)	157.65(15)
O(1)-C(2)-C(3)-C(8)	-26.18(18)
O(7)-C(3)-C(4)-O(3)	-174.26(11)
C(8)-C(3)-C(4)-O(3)	72.25(16)
C(2)-C(3)-C(4)-O(3)	-56.29(15)
O(7)-C(3)-C(4)-C(5)	62.76(16)
C(8)-C(3)-C(4)-C(5)	-50.72(17)
C(2)-C(3)-C(4)-C(5)	-179.27(12)
O(3)-C(4)-C(5)-O(4)	43.98(16)
C(3)-C(4)-C(5)-O(4)	166.94(13)
O(3)-C(4)-C(5)-C(6)	-79.91(16)
C(3)-C(4)-C(5)-C(6)	43.05(17)
C(7)-O(5)-C(6)-F	110.62(16)
C(7)-O(5)-C(6)-C(5)	-116.16(17)
O(4)-C(5)-C(6)-F	61.12(17)
C(4)-C(5)-C(6)-F	-175.01(13)
O(4)-C(5)-C(6)-O(5)	-72.41(18)
C(4)-C(5)-C(6)-O(5)	51.46(19)
O(4)-C(5)-C(6)-C(7)	-146.09(15)
C(4)-C(5)-C(6)-C(7)	-22.2(2)
F-C(6)-C(7)-O(5)	-102.71(15)
C(5)-C(6)-C(7)-O(5)	105.91(16)
F-C(6)-C(7)-C(8)	156.74(14)
O(5)-C(6)-C(7)-C(8)	-100.54(15)
C(5)-C(6)-C(7)-C(8)	5.4(2)
C(6)-O(5)-C(7)-C(8)	113.16(15)
C(9)-O(6)-C(8)-C(7)	94.82(15)
C(9)-O(6)-C(8)-C(3)	-25.42(15)

C(6)-C(7)-C(8)-O(6)	-122.71(15)
O(5)-C(7)-C(8)-O(6)	172.19(12)
C(6)-C(7)-C(8)-C(3)	-9.1(2)
O(5)-C(7)-C(8)-C(3)	-74.22(15)
O(7)-C(3)-C(8)-O(6)	34.05(14)
C(4)-C(3)-C(8)-O(6)	149.78(12)
C(2)-C(3)-C(8)-O(6)	-86.01(14)
O(7)-C(3)-C(8)-C(7)	-84.03(14)
C(4)-C(3)-C(8)-C(7)	31.70(18)
C(2)-C(3)-C(8)-C(7)	155.91(13)
C(8)-O(6)-C(9)-O(7)	7.25(16)
C(8)-O(6)-C(9)-C(11)	125.77(15)
C(8)-O(6)-C(9)-C(10)	-108.65(16)
C(3)-O(7)-C(9)-O(6)	16.16(16)
C(3)-O(7)-C(9)-C(11)	-100.94(15)
C(3)-O(7)-C(9)-C(10)	134.32(15)

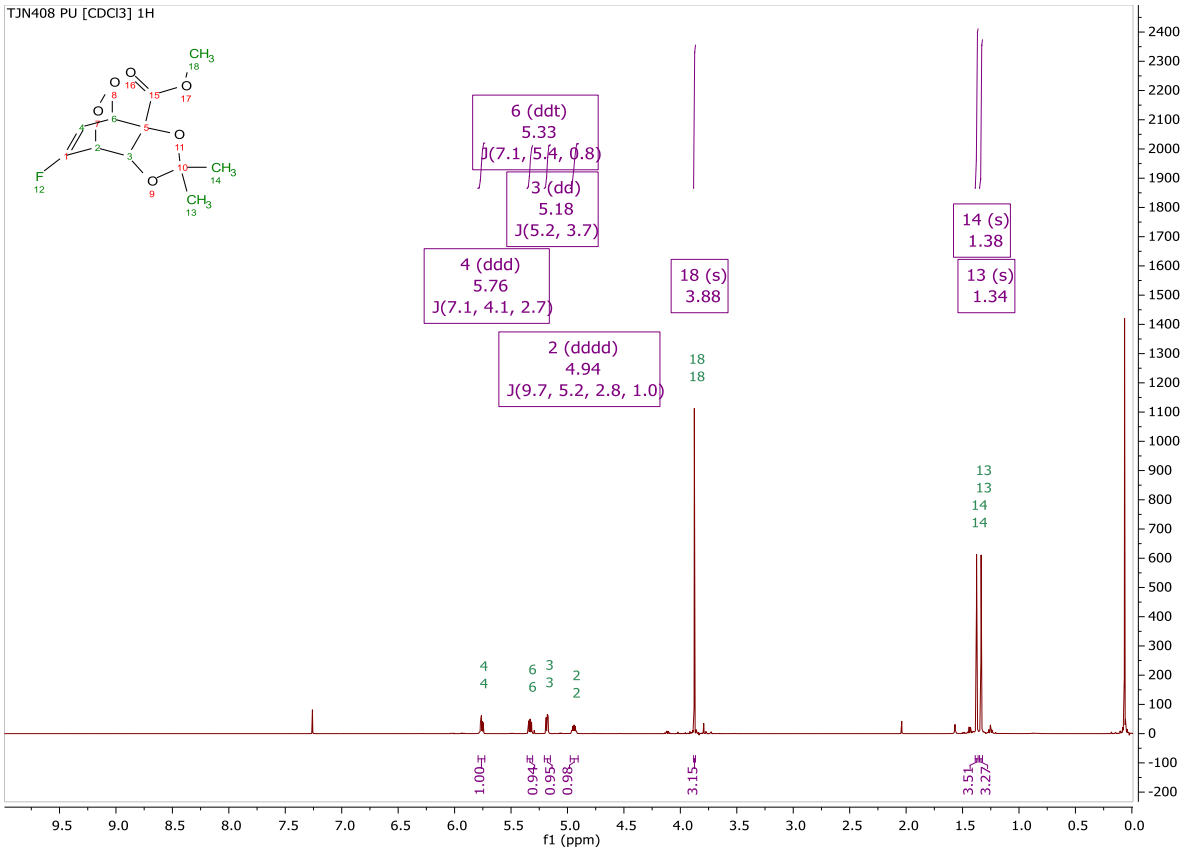
Table 8. Hydrogen bonds for s18sel11 [Å and °].

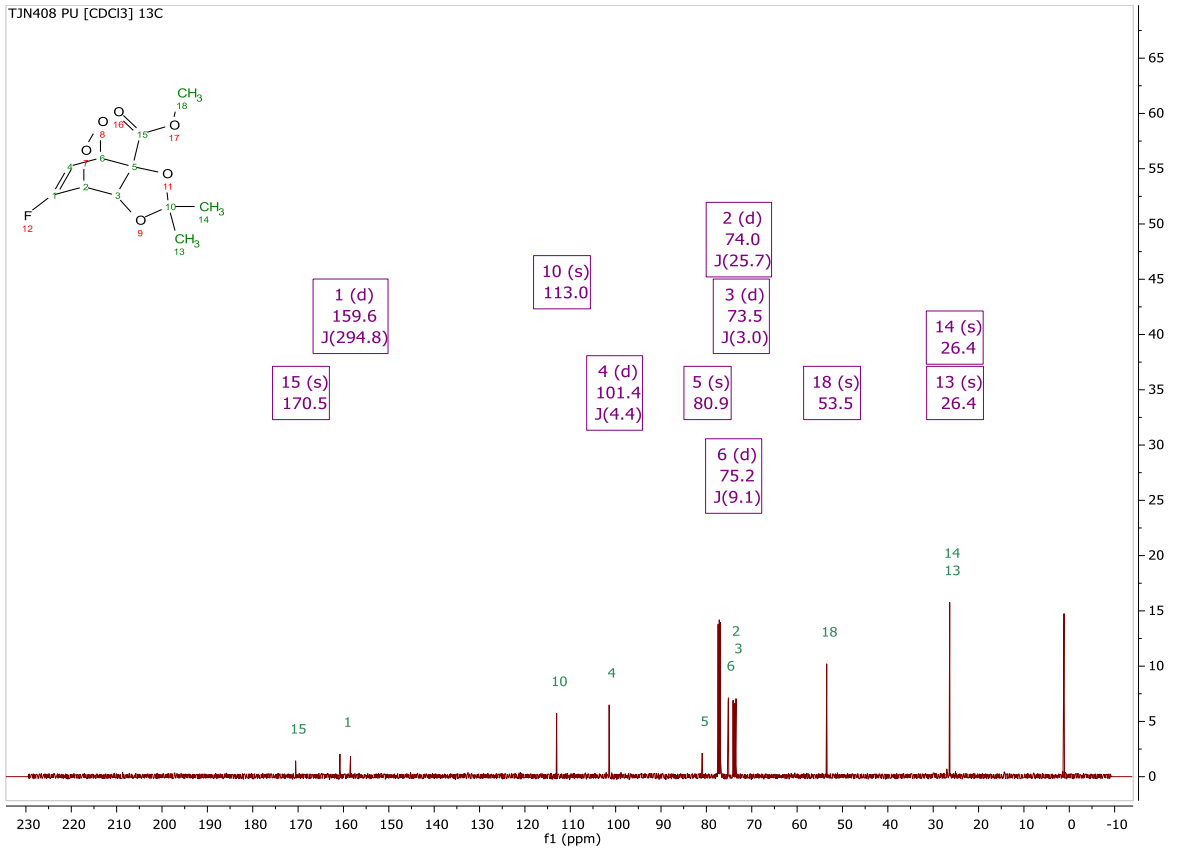
D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(3)#1	0.85(3)	2.33(3)	3.0516(6)	142(2)
O(3)-H(3)...O(5)#1	0.85(3)	2.26(3)	2.9432(16)	137(2)
O(4)-H(4)...O(2)#2	0.81(3)	2.37(3)	3.1320(17)	157(2)
O(4)-H(4)...O(3)	0.81(3)	2.23(2)	2.7026(16)	117(2)

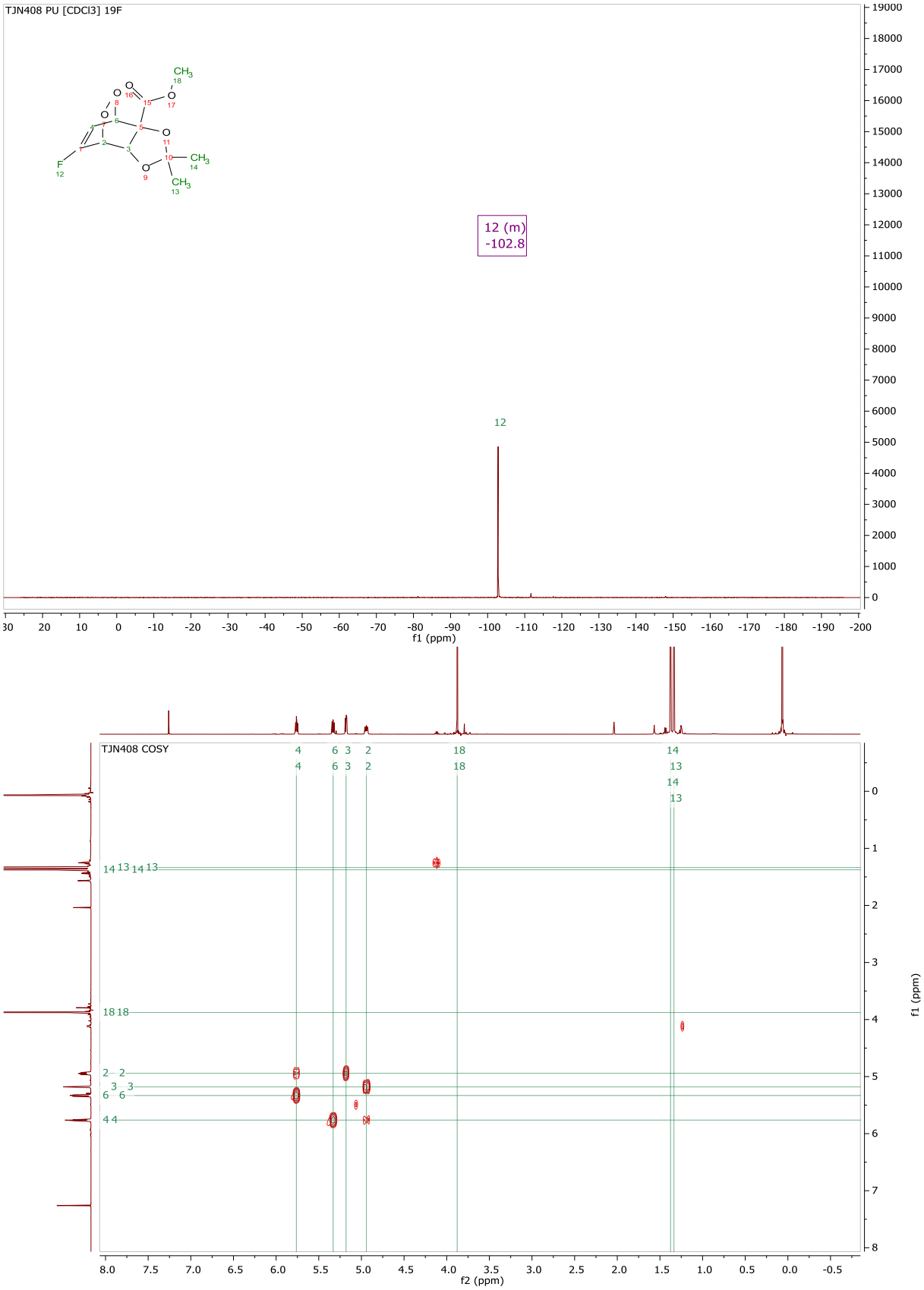
Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+1/2,-z+1 #2 x+1/2,-y+1/2,-z+1

Methyl (3a*R*,4*R*,7*R*,7a*R*)-6-fluoro-2,2-dimethyl-7,7a-dihydro-4,7-epidioxybenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-47



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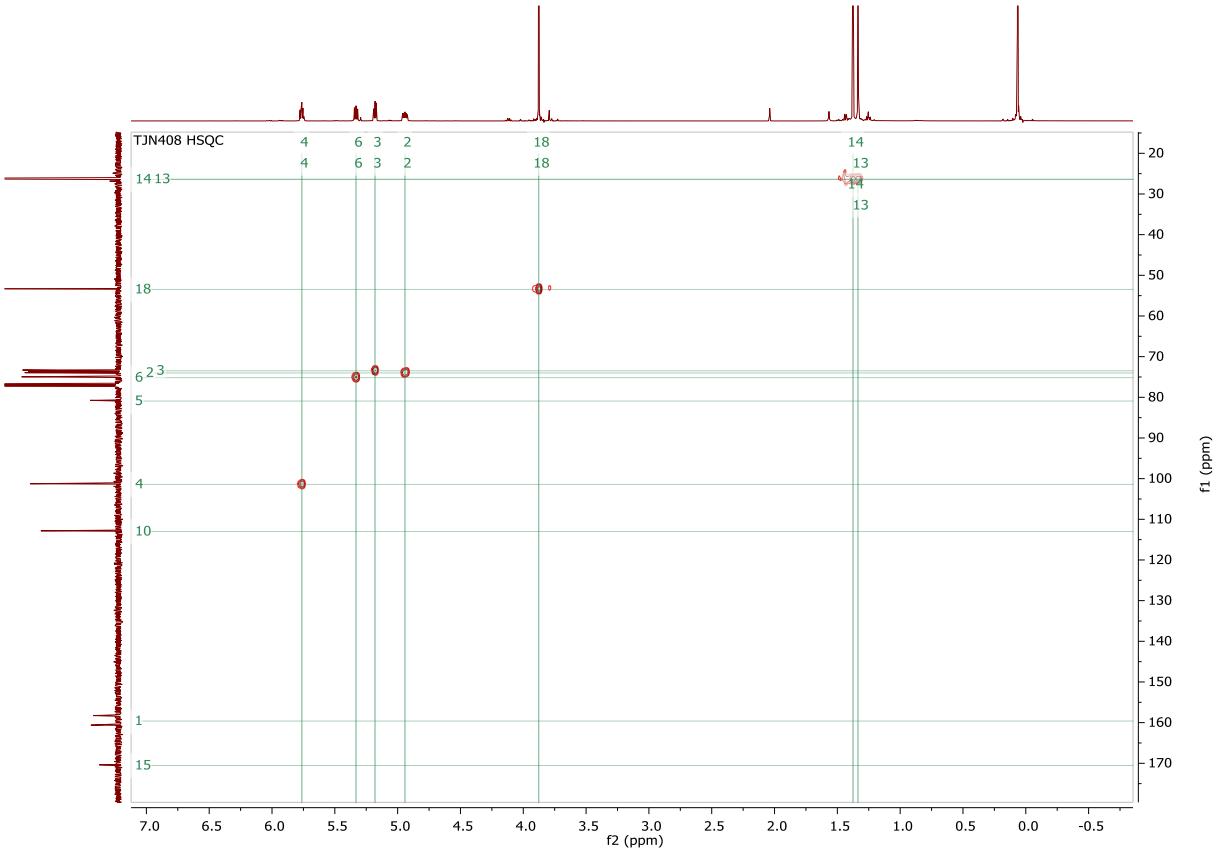
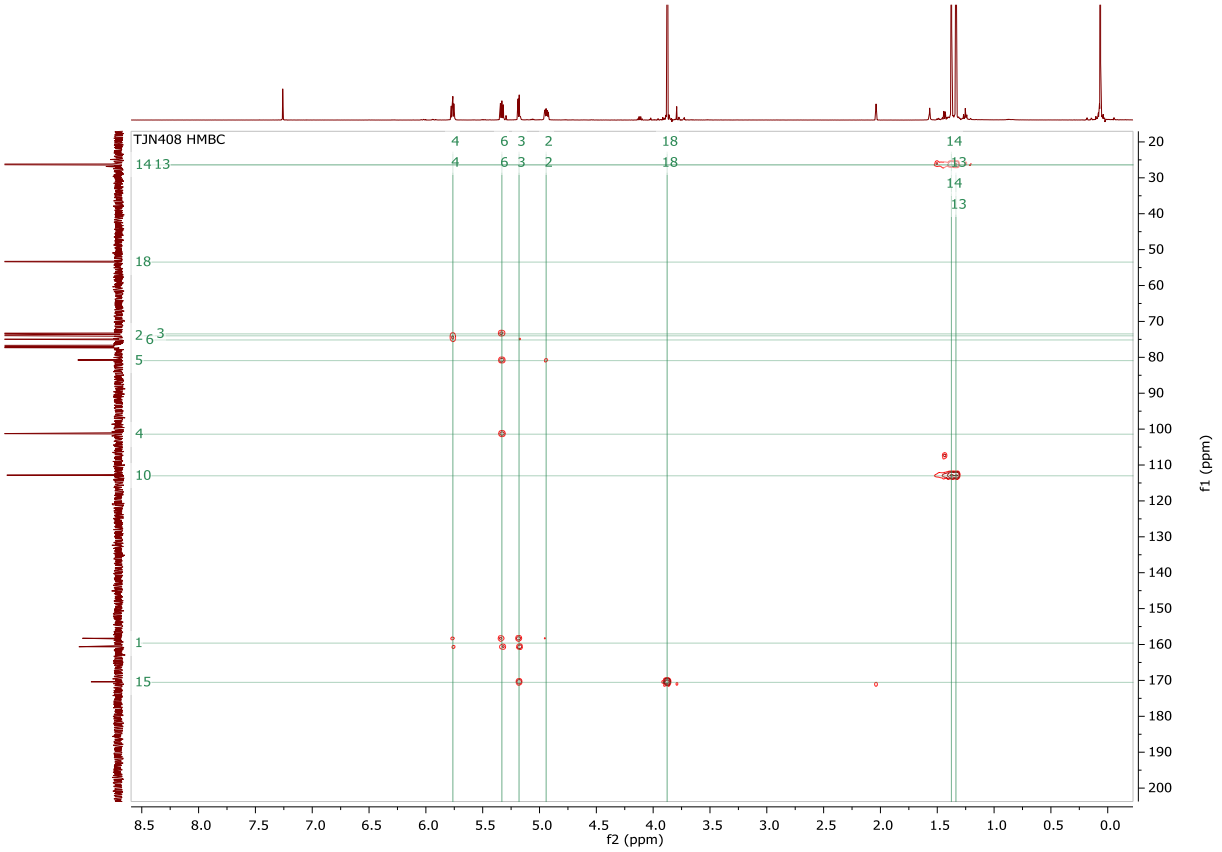
f2 (ppm)
f1 (ppm)

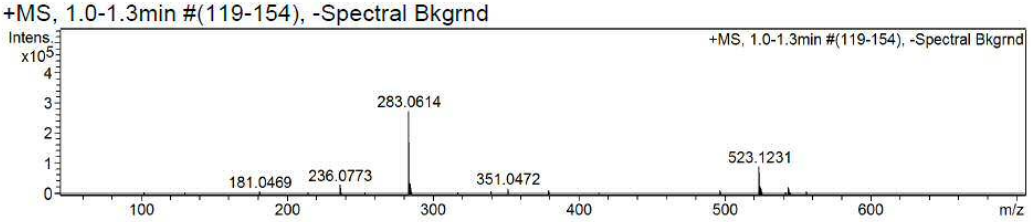

TJN408 HSQC
f2 (ppm)
f1 (ppm)


TJN408 HMBC
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

Sample-ID	tn_sel_TJN408	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN408_353069_92_01_58633.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	25/08/2017 15:10:18
Ionisation Mode	positive electrospray (ESI)		

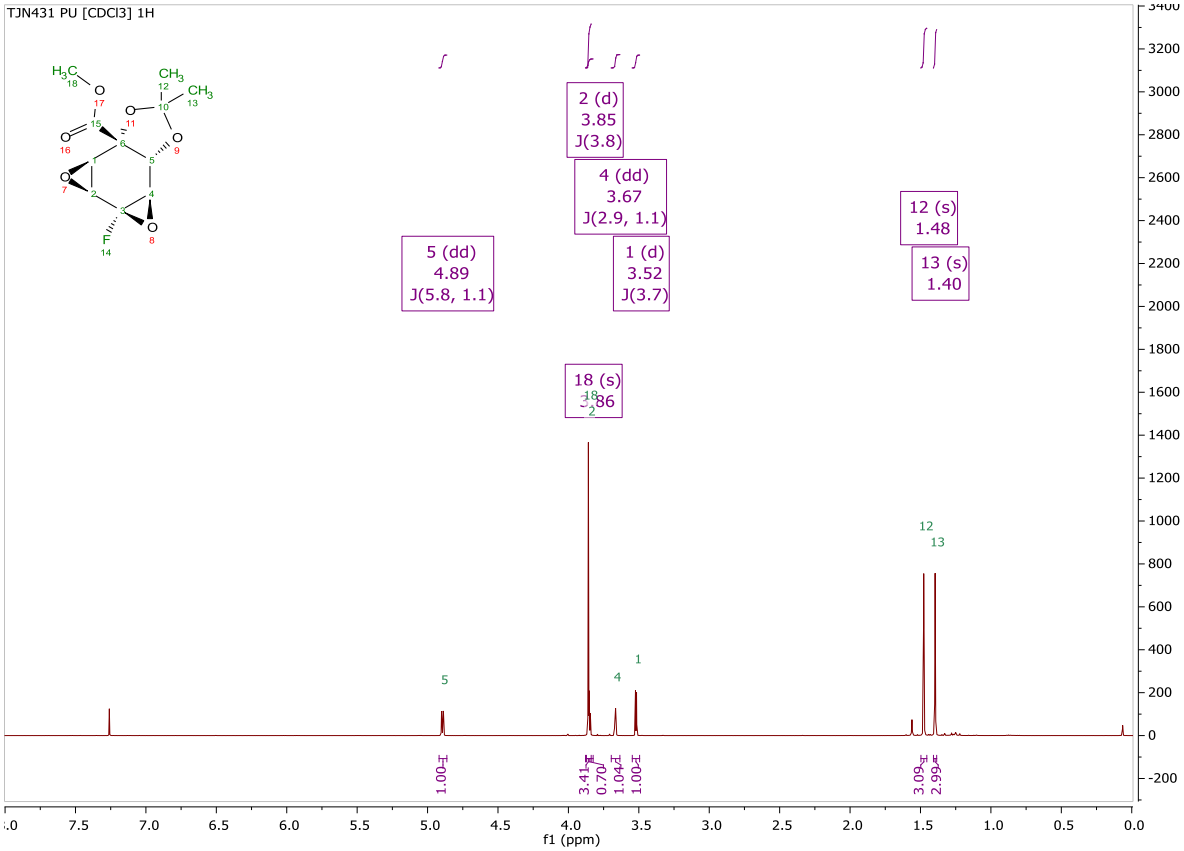
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

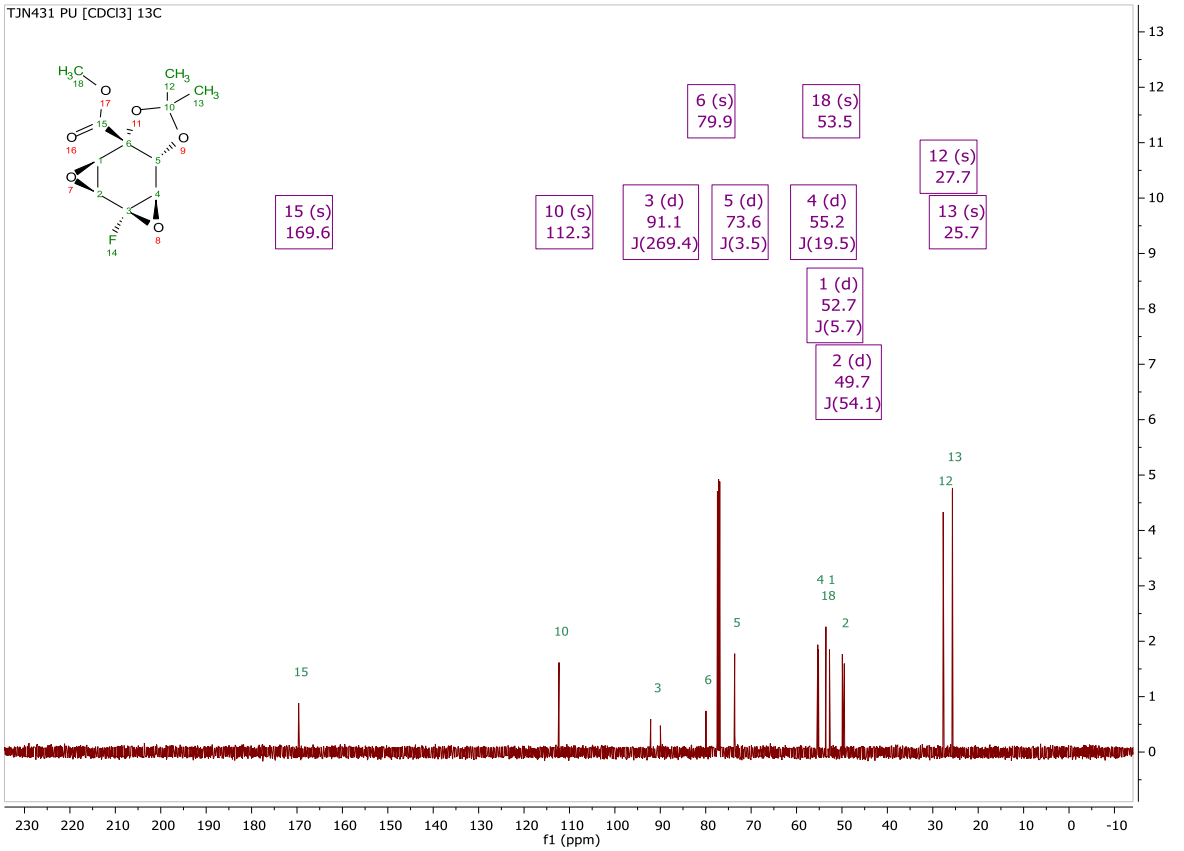


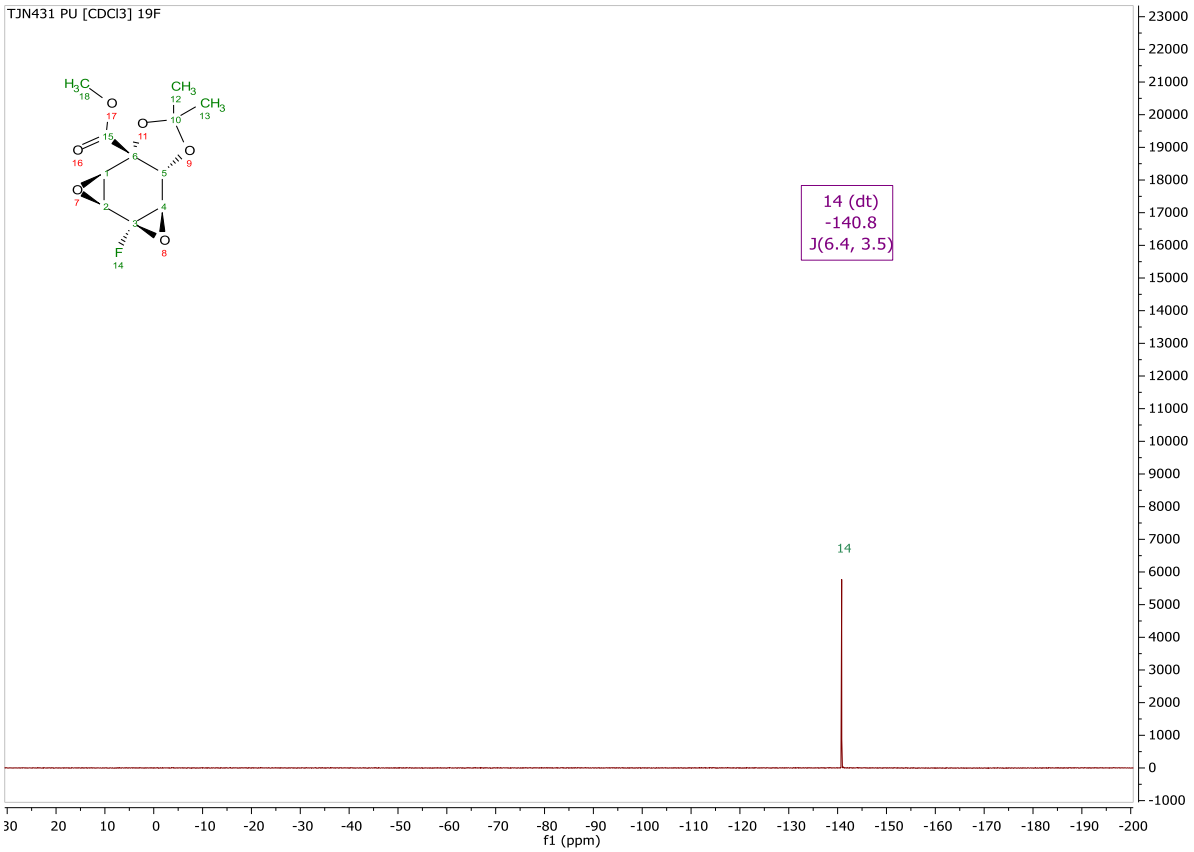
#	m/z	I	I %	Area	S/N
1	236.0773	27918	10.3	668	1970.6
2	283.0614	271725	100.0	14759	6937.0
3	284.0610	32795	12.1	1527	824.7
4	285.0657	6956	2.6	322	172.3
5	351.0472	17467	6.4	1091	1005.5
6	379.1158	9280	3.4	599	639.1
7	496.1478	10030	3.7	847	378.7
8	523.1231	88983	32.7	9095	3142.7
9	524.1255	20808	7.7	2067	741.2
10	543.1303	19718	7.3	1945	842.1

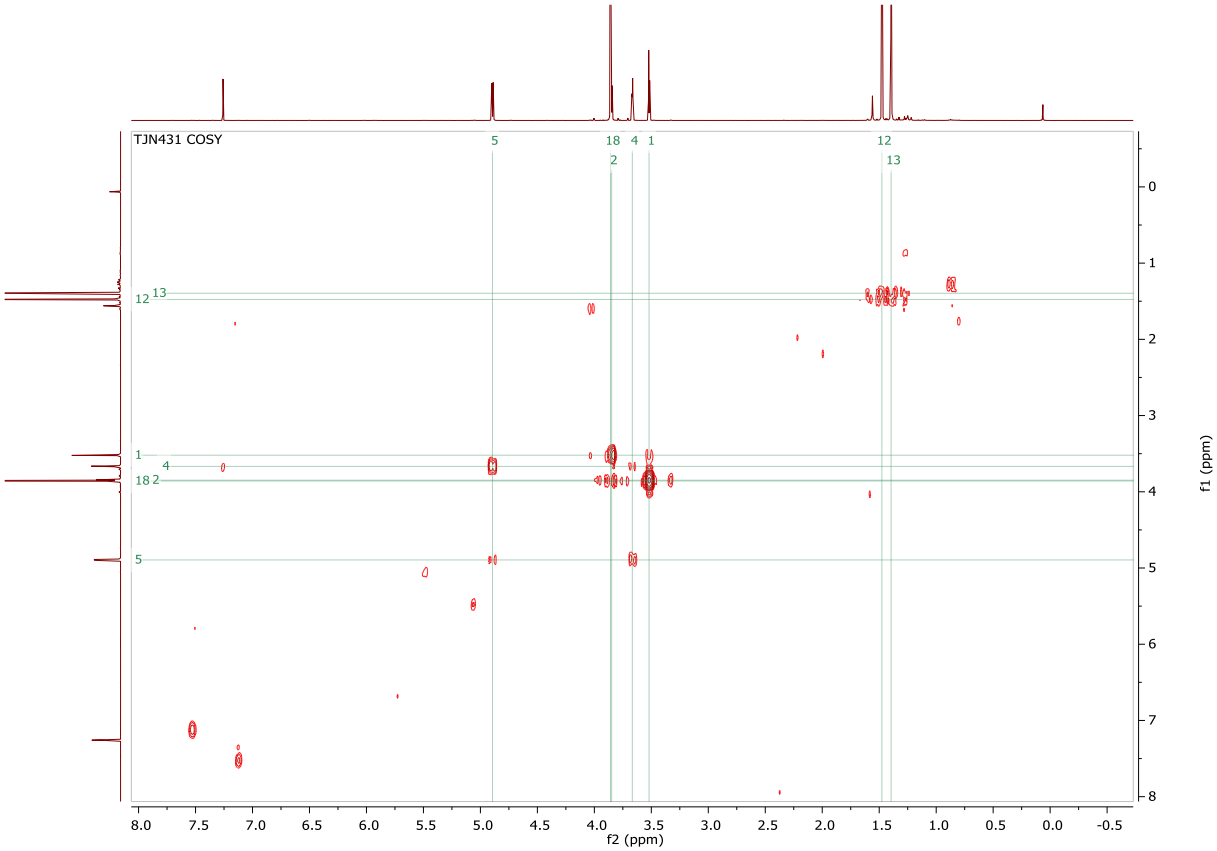
Methyl (1a*S*,1b*S*,2a*R*,2b*S*,5a*R*,5b*R*)-1a-fluoro-4,4-dimethyltetrahydrobis(oxireno)[2',3':3,4;2'',3'':5,6]benzo[1,2-d][1,3]dioxole-2b(1aH)-carboxylate

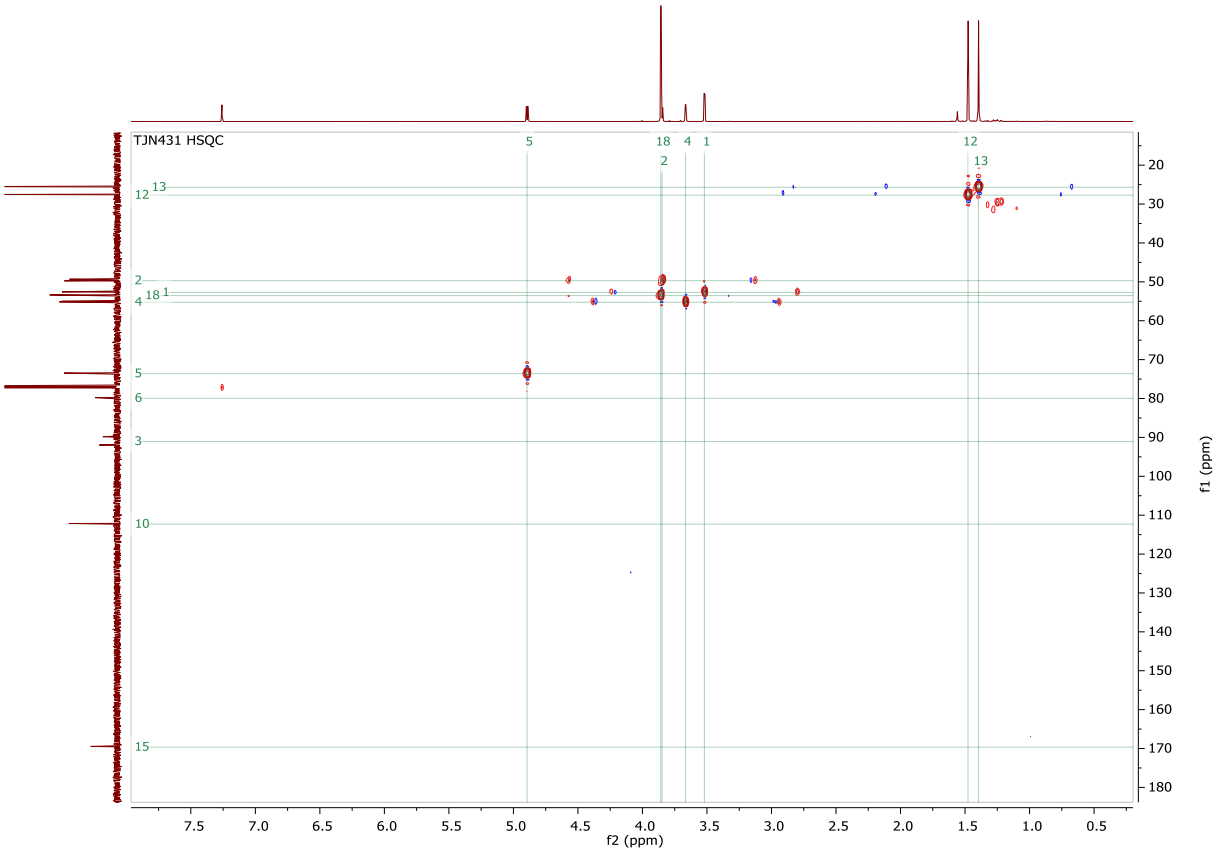
IV-48

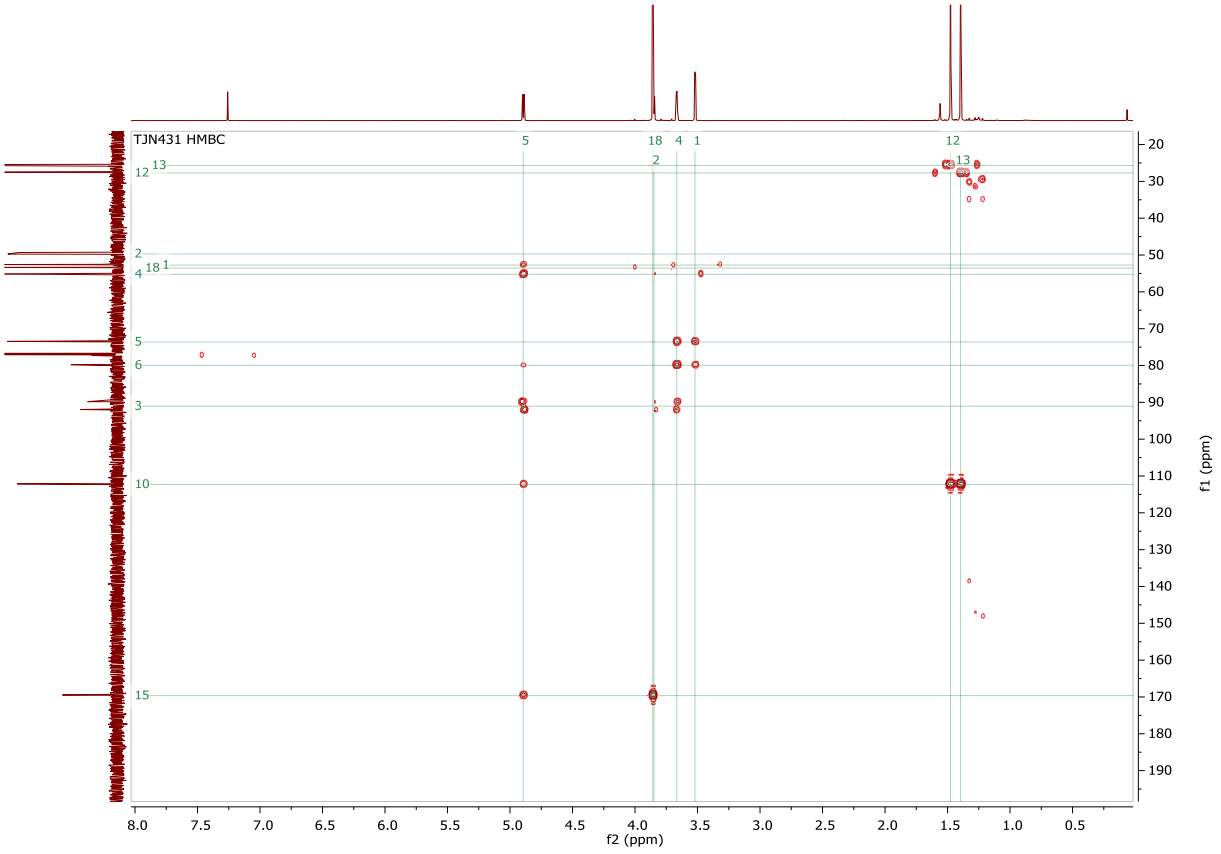





TJN431 PU [CDCl3] 19F
14 (dt)
-140.8
J(6.4, 3.5)
14
f1 (ppm)


TJN431 COSY
f2 (ppm)
f1 (ppm)

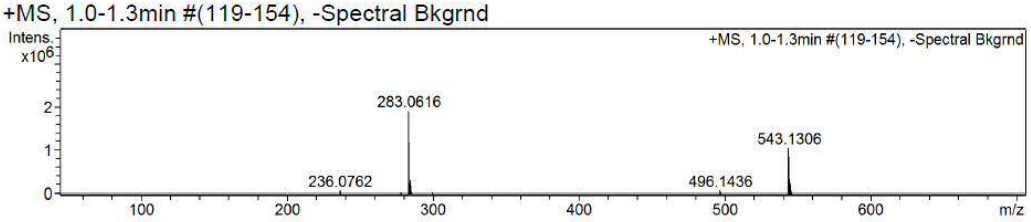

TJN431 HSQC
f2 (ppm)
f1 (ppm)


TJN431 HMBC
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

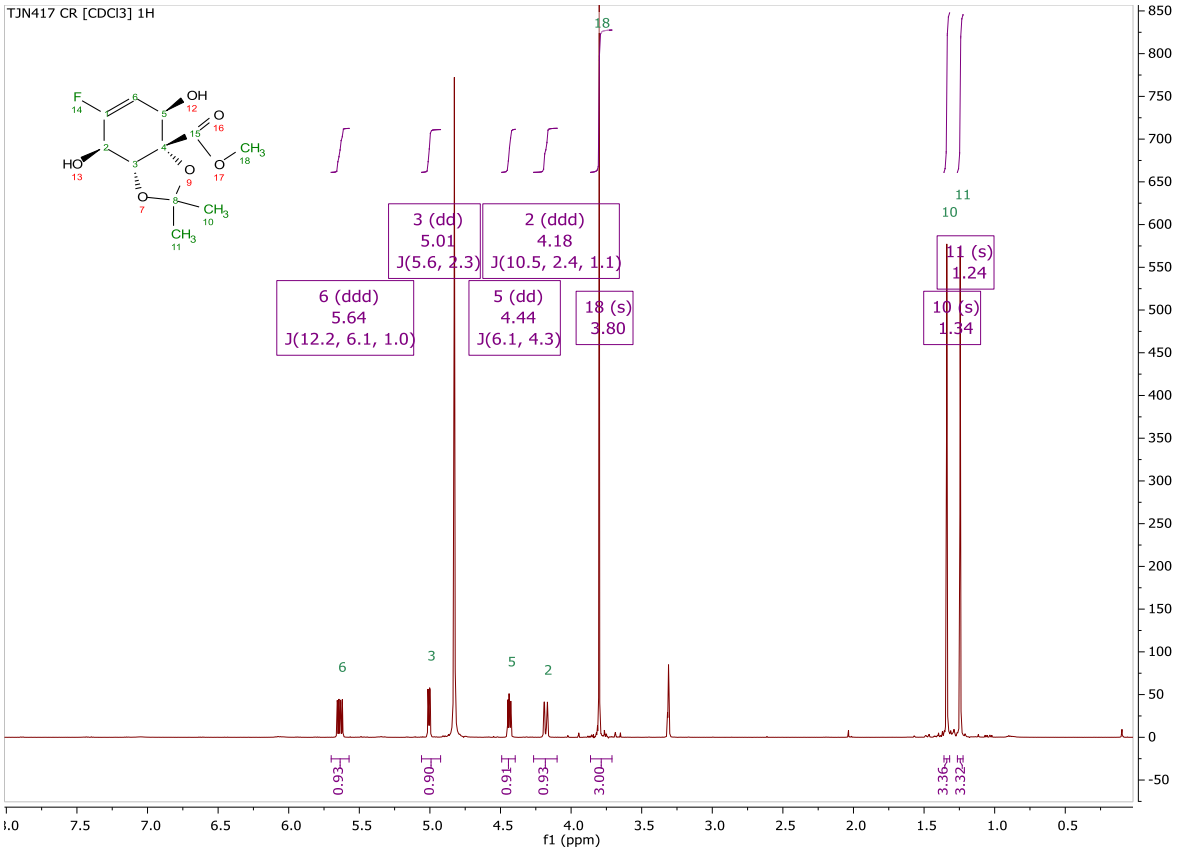
Sample-ID	tn_sel_TJN431	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN431_353534_76_01_59191.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	28/09/2017 17:47:33
Ionisation Mode	positive electrospray (ESI)		

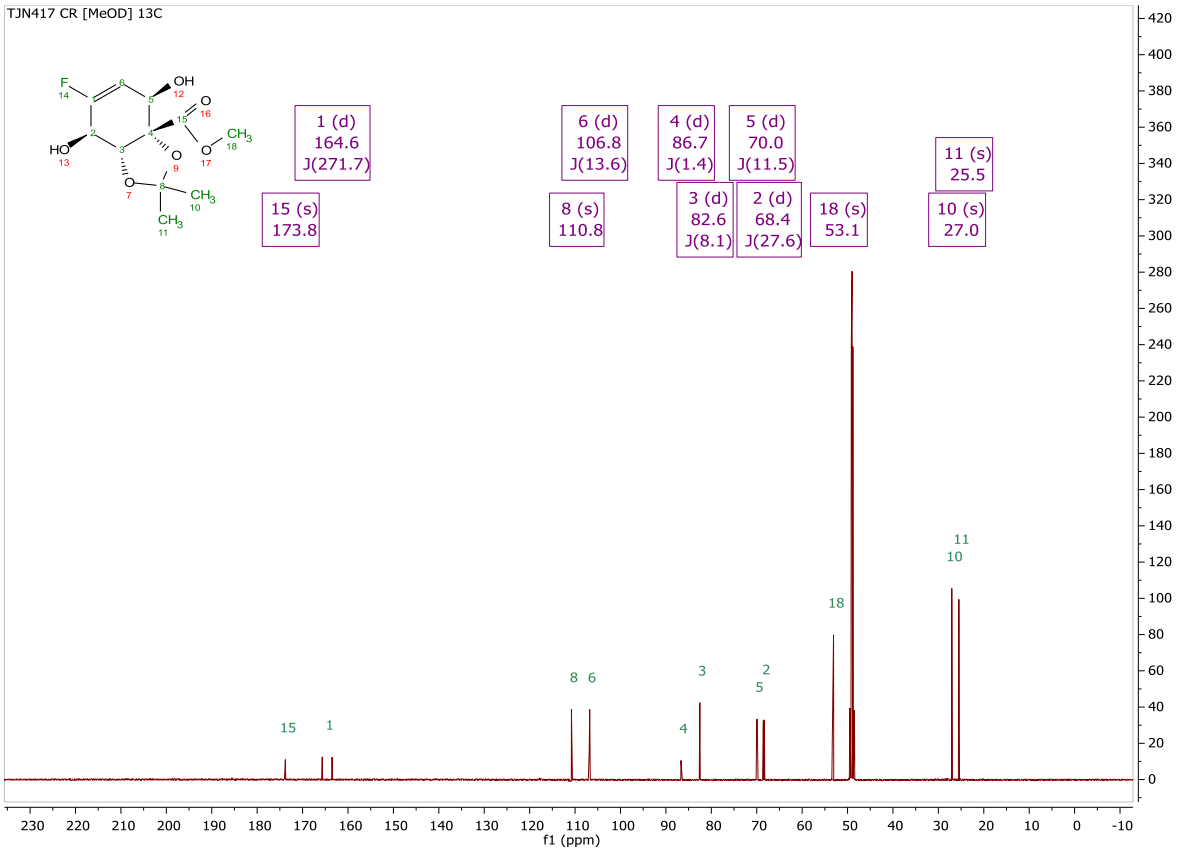
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

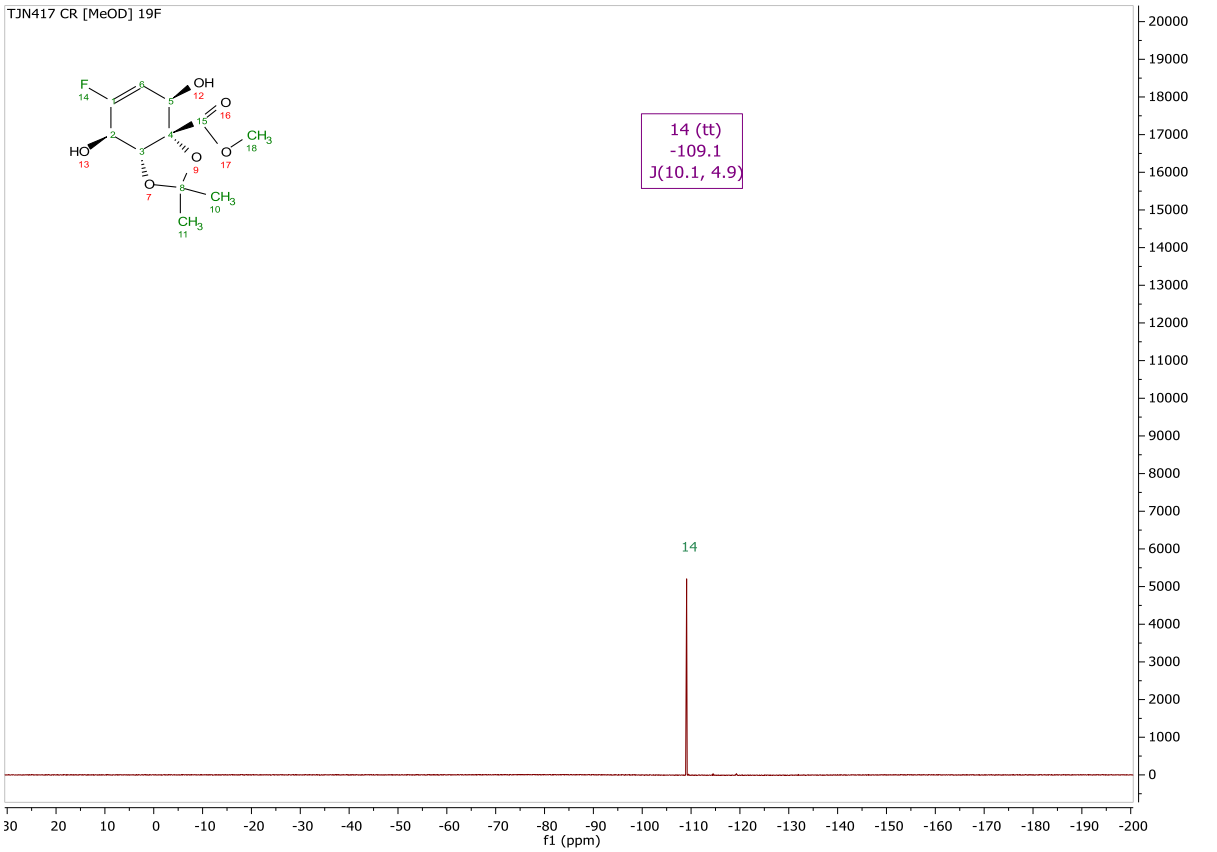


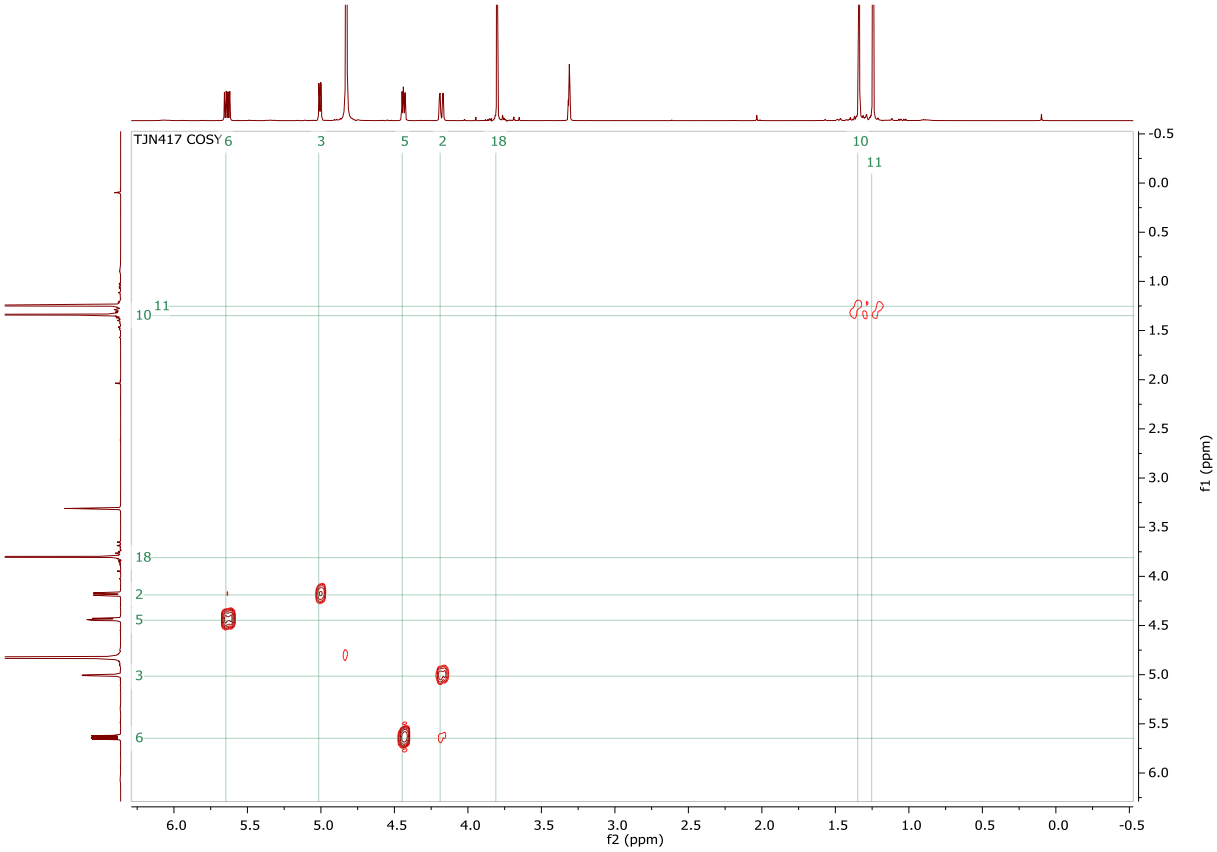
#	m/z	I	I %	Area	S/N
1	236.0762	71530	3.8	1934	1686.5
2	278.1052	20951	1.1	998	95.5
3	283.0616	1898946	100.0	138117	7795.4
4	284.0626	324055	17.1	16063	1303.7
5	285.0632	45140	2.4	2107	178.0
6	299.0332	21449	1.1	1012	110.1
7	496.1436	65120	3.4	5709	2250.8
8	543.1306	1055204	55.6	114794	8022.6
9	544.1331	258841	13.6	27117	1927.4
10	545.1363	51503	2.7	5065	375.7

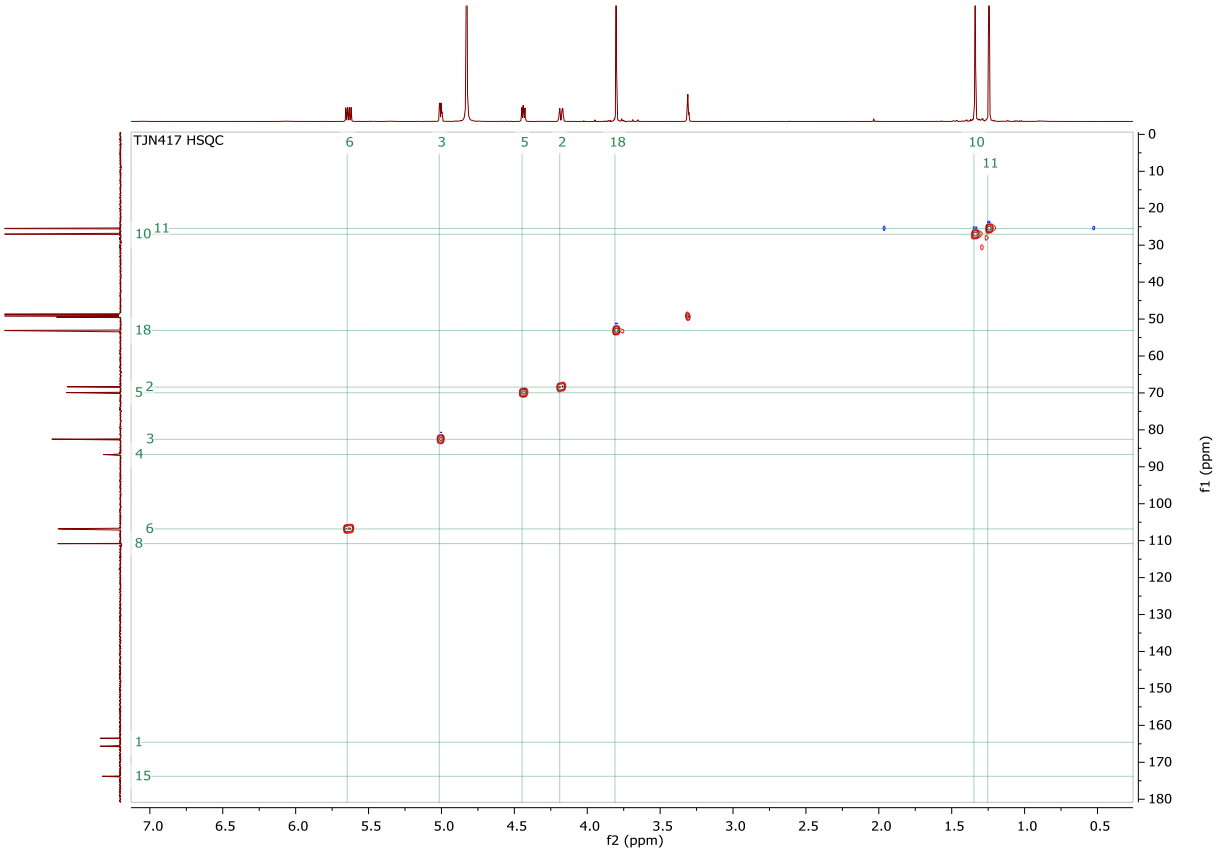
Methyl (3a*S*,4*R*,7*R*,7a*R*)-6-fluoro-4,7-dihydroxy-2,2-dimethyl-7,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-49

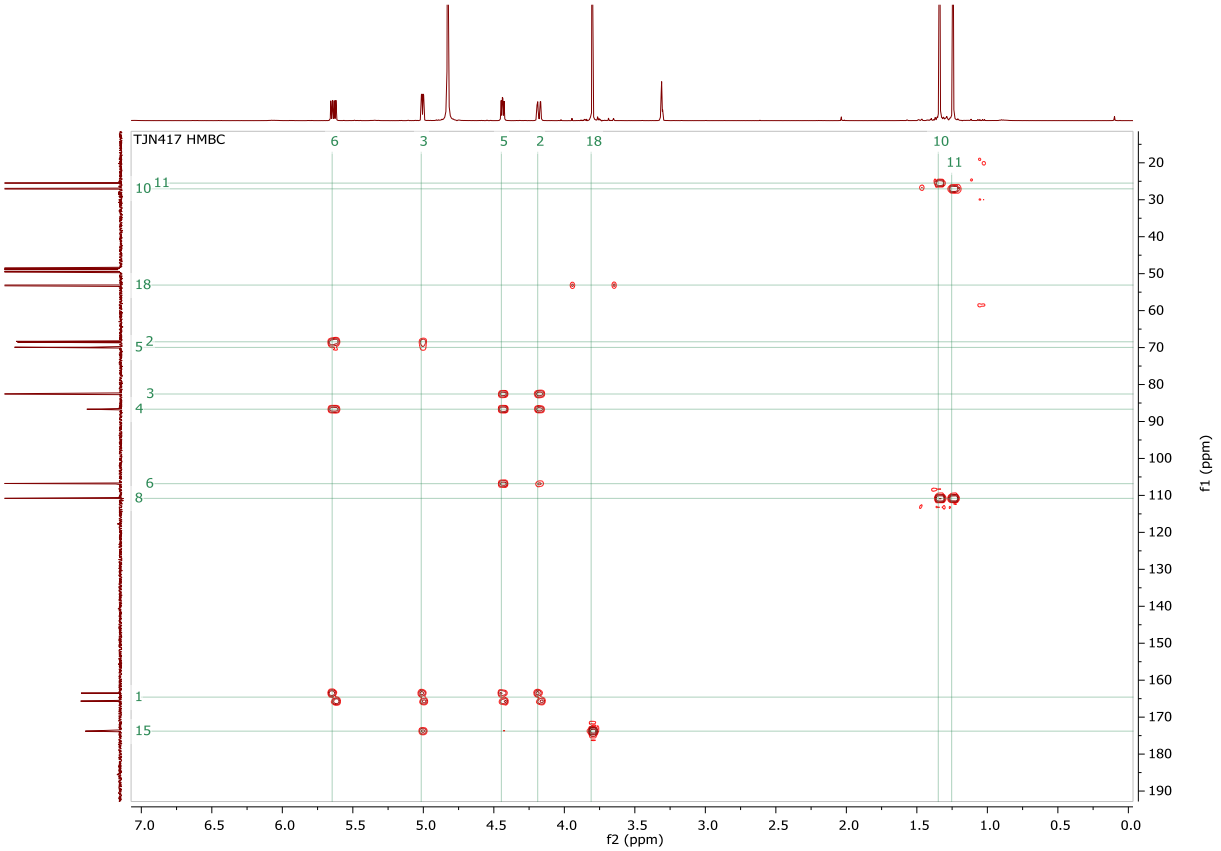





TJN417 CR [MeOD] 19F
14 (tt)
-109.1
J(10.1, 4.9)
14
f1 (ppm)


TJN417 COSY
6
3
5
2
18
10
11
f2 (ppm)
f1 (ppm)

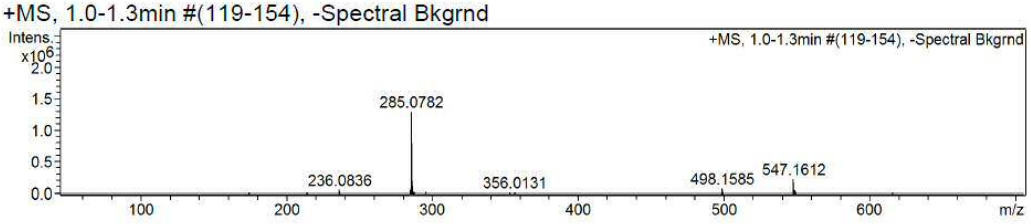

TJN417 HSQC
6
3
5
2
18
10
11
1
15
f2 (ppm)
f1 (ppm)


TJN417 HMBC
6
3
5
2
18
10
11
1
15
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

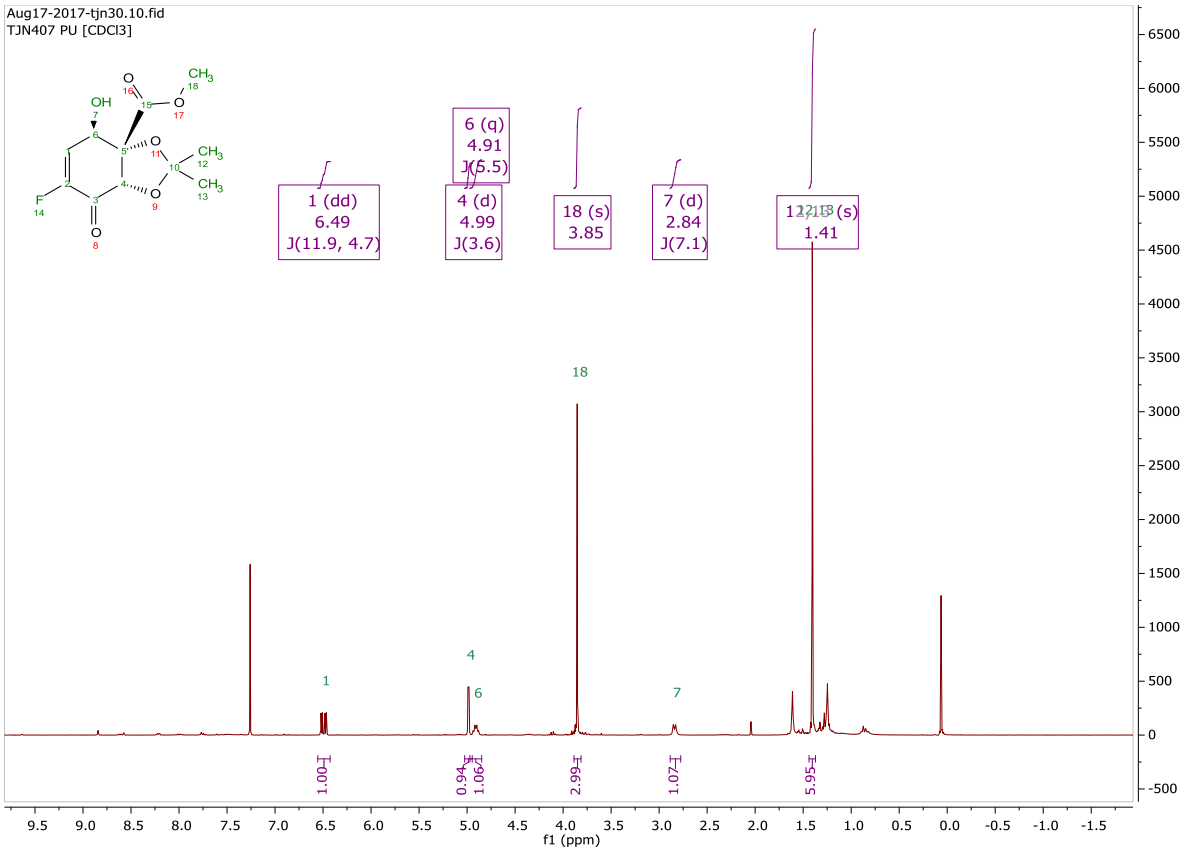
Sample-ID	tn_sel_TJN417	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN417_353225_53_01_58827.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	07/09/2017 10:07:35
Ionisation Mode	positive electrospray (ESI)		

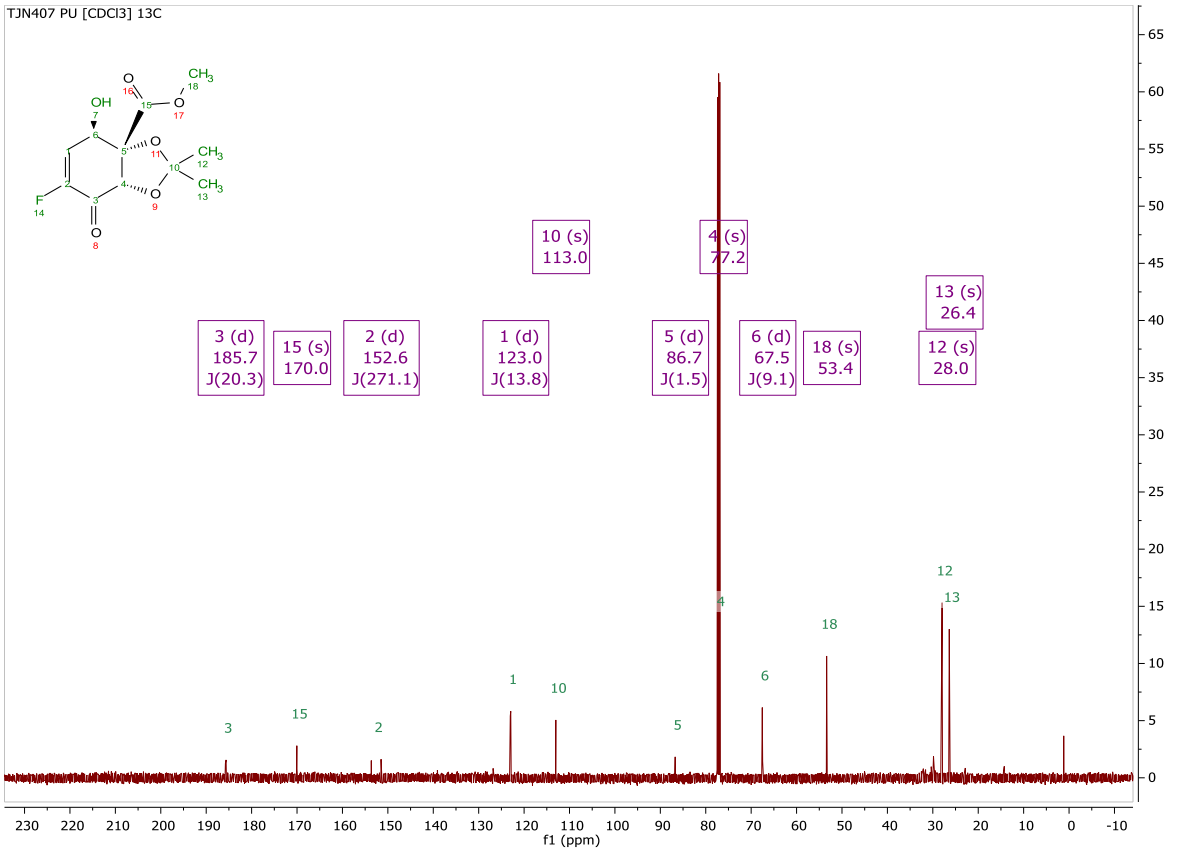
+MS, 1.0-1.3min #(119-154), -Spectral Bkgrnd

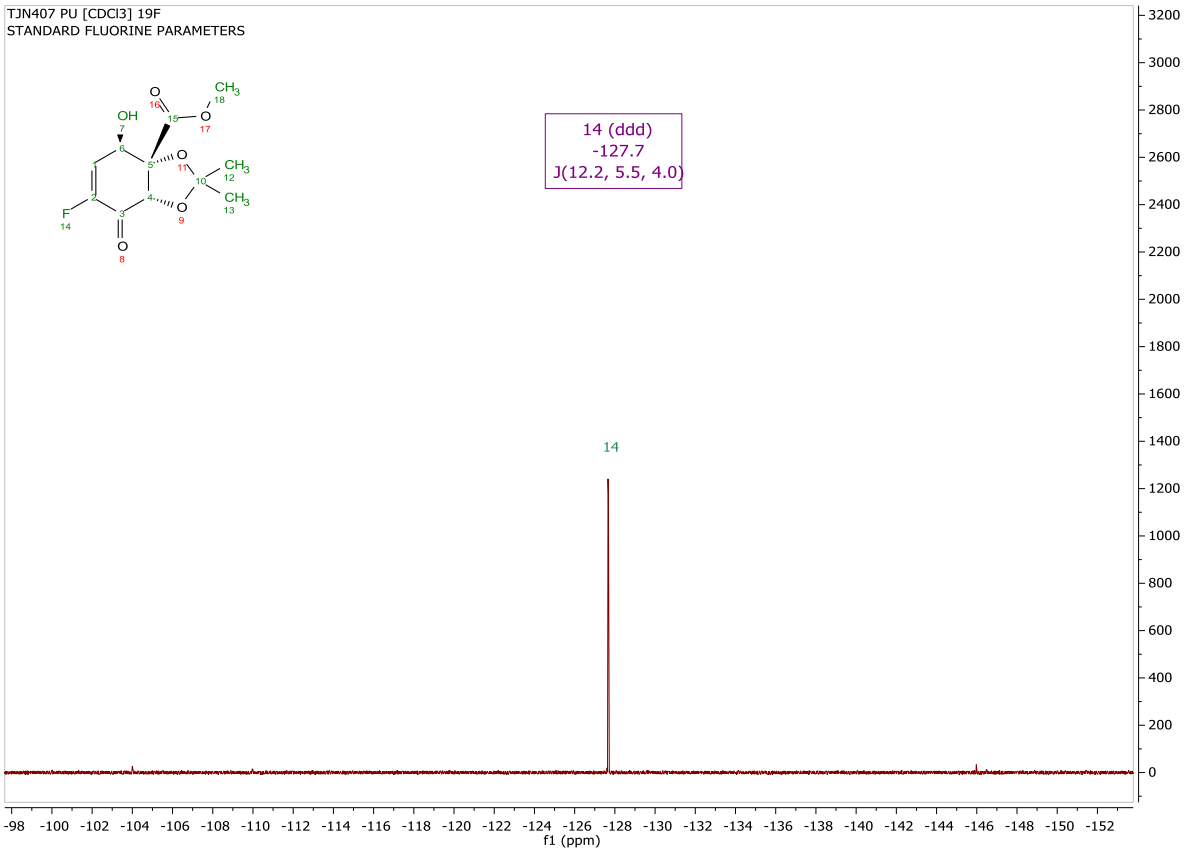


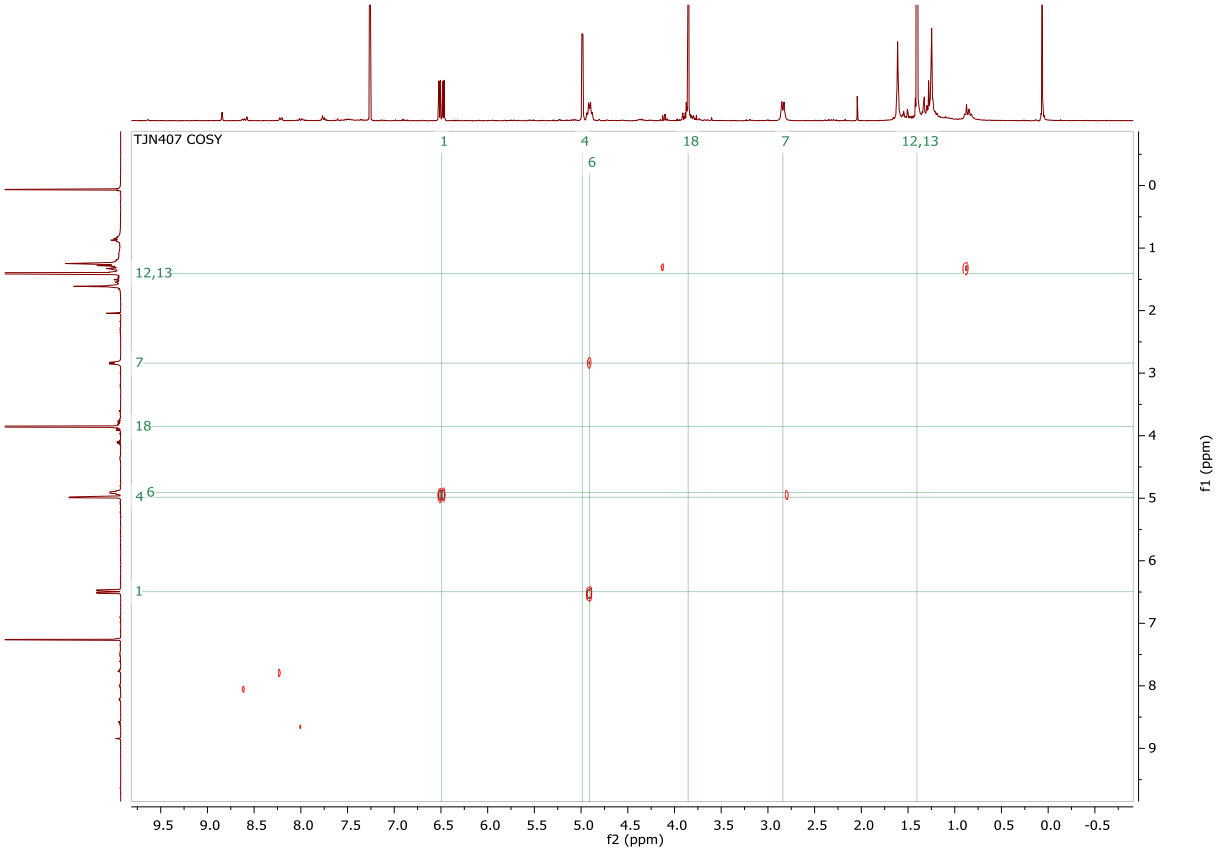
#	m/z	I	I %	Area	S/N
1	236.0836	61881	4.8	1209	1427.3
2	285.0782	1298676	100.0	88949	8211.2
3	286.0787	210039	16.2	11079	1305.4
4	287.0802	30710	2.4	1577	188.1
5	295.0800	30651	2.4	1640	224.3
6	353.0631	27894	2.1	1767	970.4
7	356.0131	27950	2.2	1777	923.3
8	498.1585	82132	6.3	7467	3487.4
9	547.1612	231335	17.8	25447	3432.0
10	548.1644	56569	4.4	6037	826.0

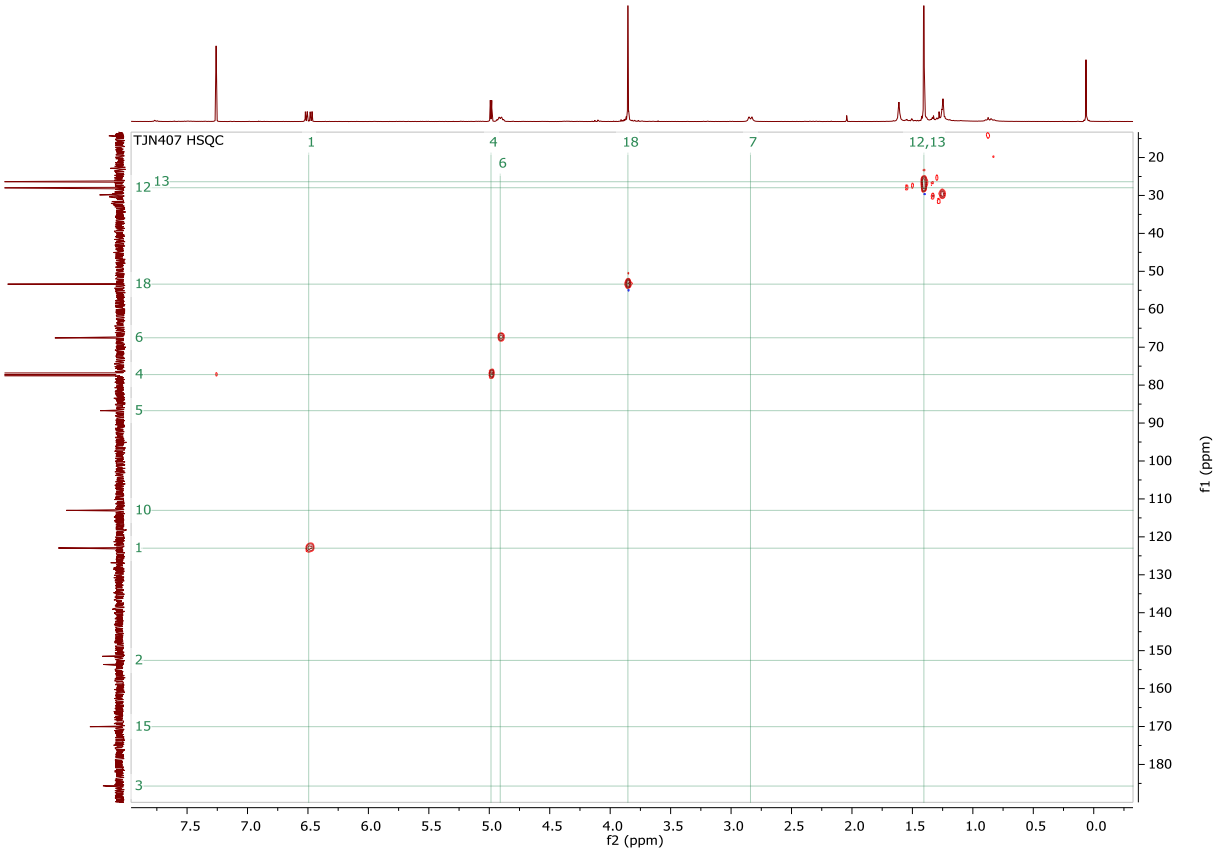
Methyl (3a*S*,4*R*,7a*S*)-6-fluoro-4-hydroxy-2,2-dimethyl-7-oxo-7,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-50

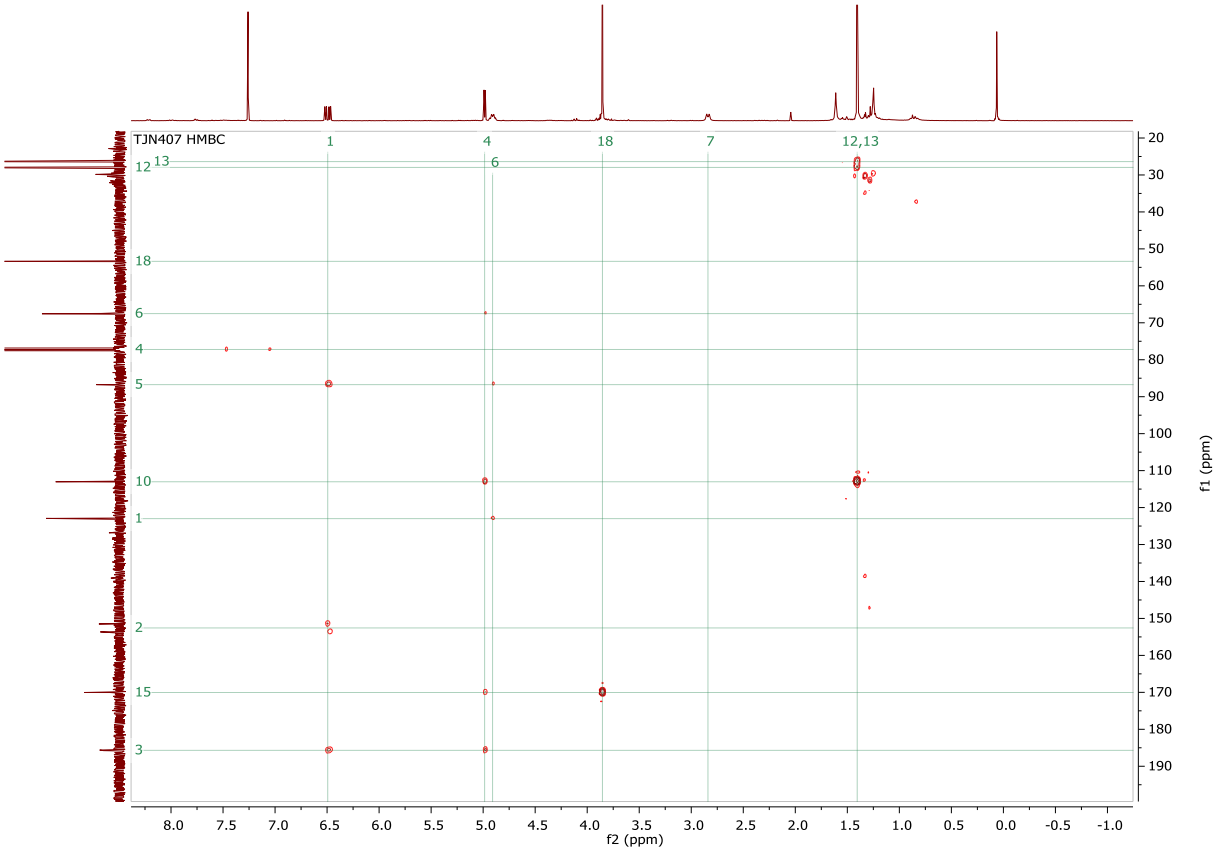





TJN407 PU [CDCl3] 19F
STANDARD FLUORINE PARAMETERS
14 (ddd)
-127.7
J(12.2, 5.5, 4.0)
14
f1 (ppm)


TJN407 COSY
1
4
18
7
12,13
6
f2 (ppm)
f1 (ppm)

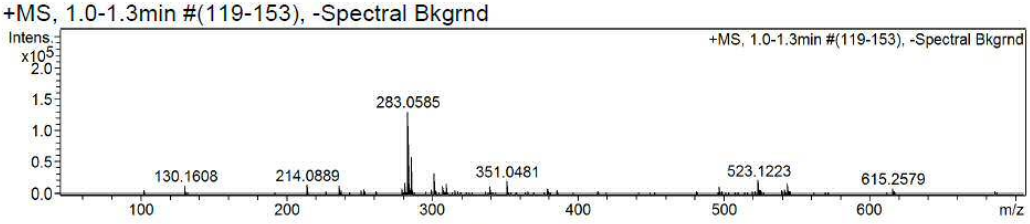

TJN407 HSQC
1
4
18
7
12,13
6
13
12
18
6
4
5
10
1
2
15
3
f2 (ppm)
f1 (ppm)


TJN407 HMBC
1
4
18
7
12,13
6
13
12
18
6
4
5
10
1
2
15
3
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

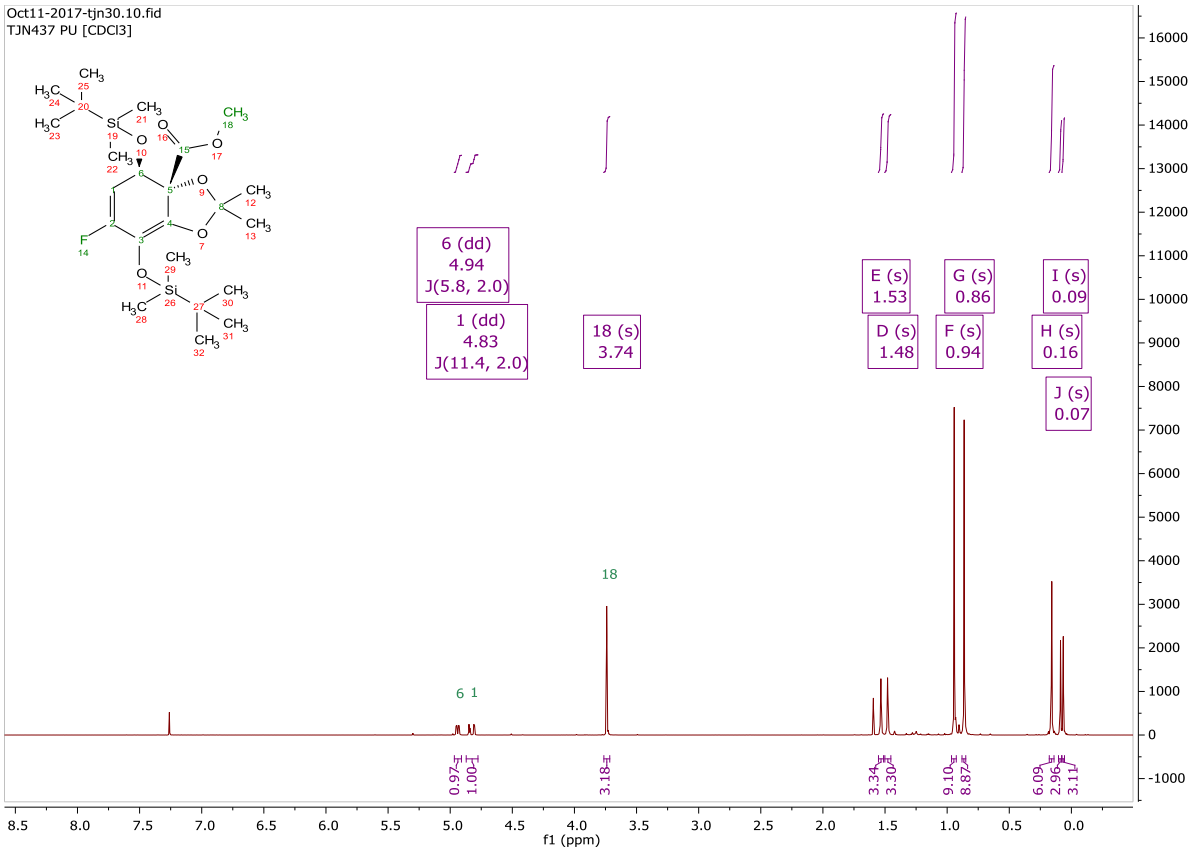
Sample-ID	tn_sel_TJN407	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN407_352975_15_01_58564.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to500 loop inj.m	Acquisition Date	24/08/2017 10:57:38
Ionisation Mode	positive electrospray (ESI)		

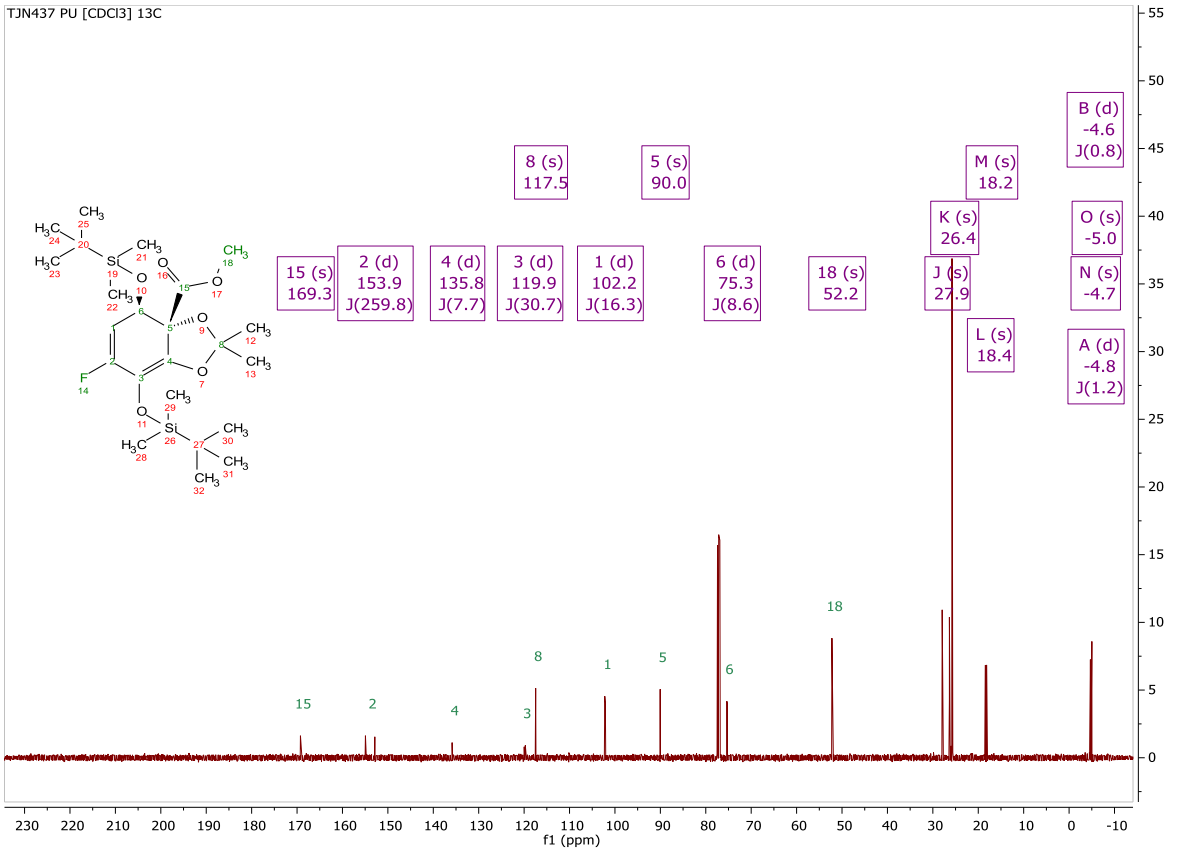
+MS, 1.0-1.3min #(119-153), -Spectral Bkgrnd

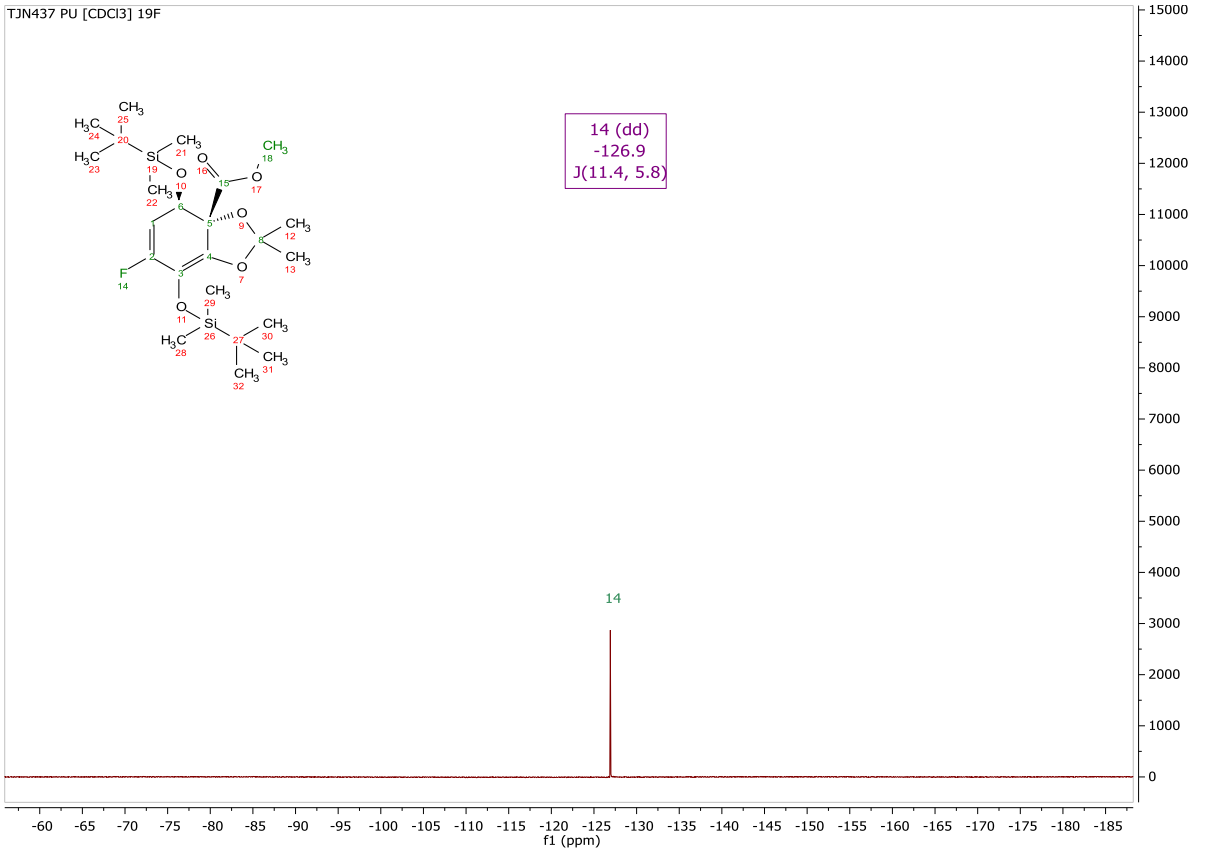


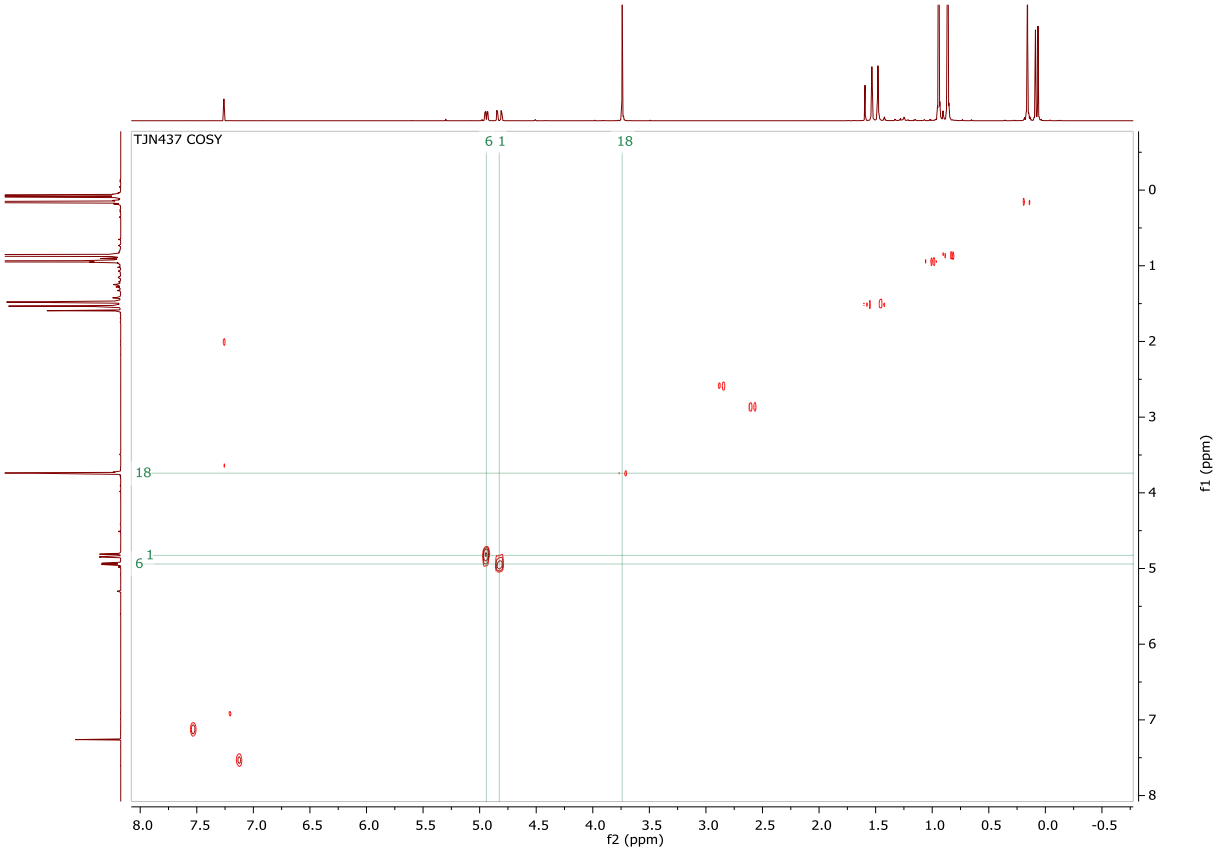
#	m/z	I	I %	Area	S/N
1	214.0889	13648	10.5	409	625.3
2	281.0638	17120	13.1	923	184.3
3	283.0585	130290	100.0	7091	1361.7
4	284.0615	15974	12.3	820	163.9
5	285.0740	57327	44.0	3069	580.5
6	301.0744	32764	25.1	1840	368.8
7	309.0947	15057	11.6	857	184.4
8	351.0481	19653	15.1	1310	332.1
9	523.1223	21438	16.5	2178	319.3
10	543.1286	16159	12.4	1698	253.0

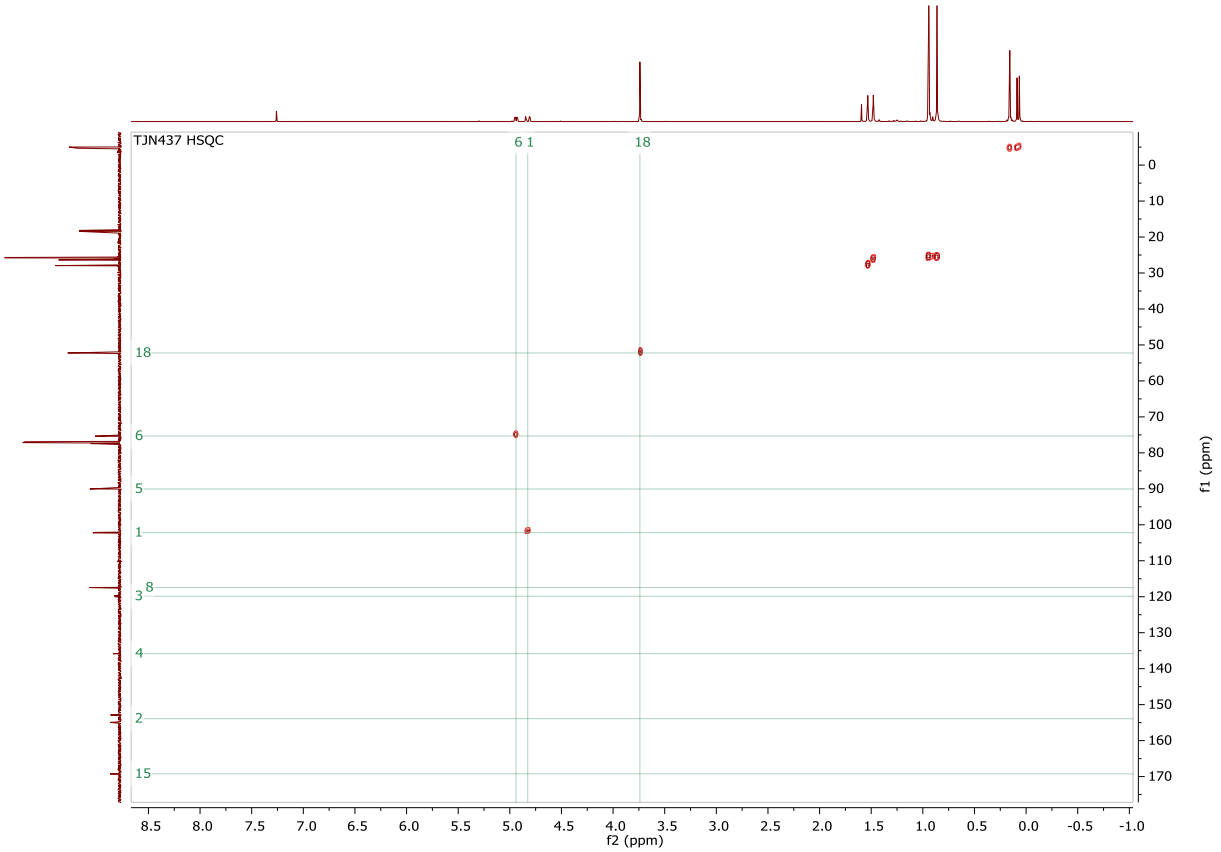
Methyl (3a*R*,4*R*,7a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-6-fluoro-2,2-dimethyl-7-oxo-7,7a-dihydrobenzo[d][1,3]dioxole-3a(4H)-carboxylate IV-54

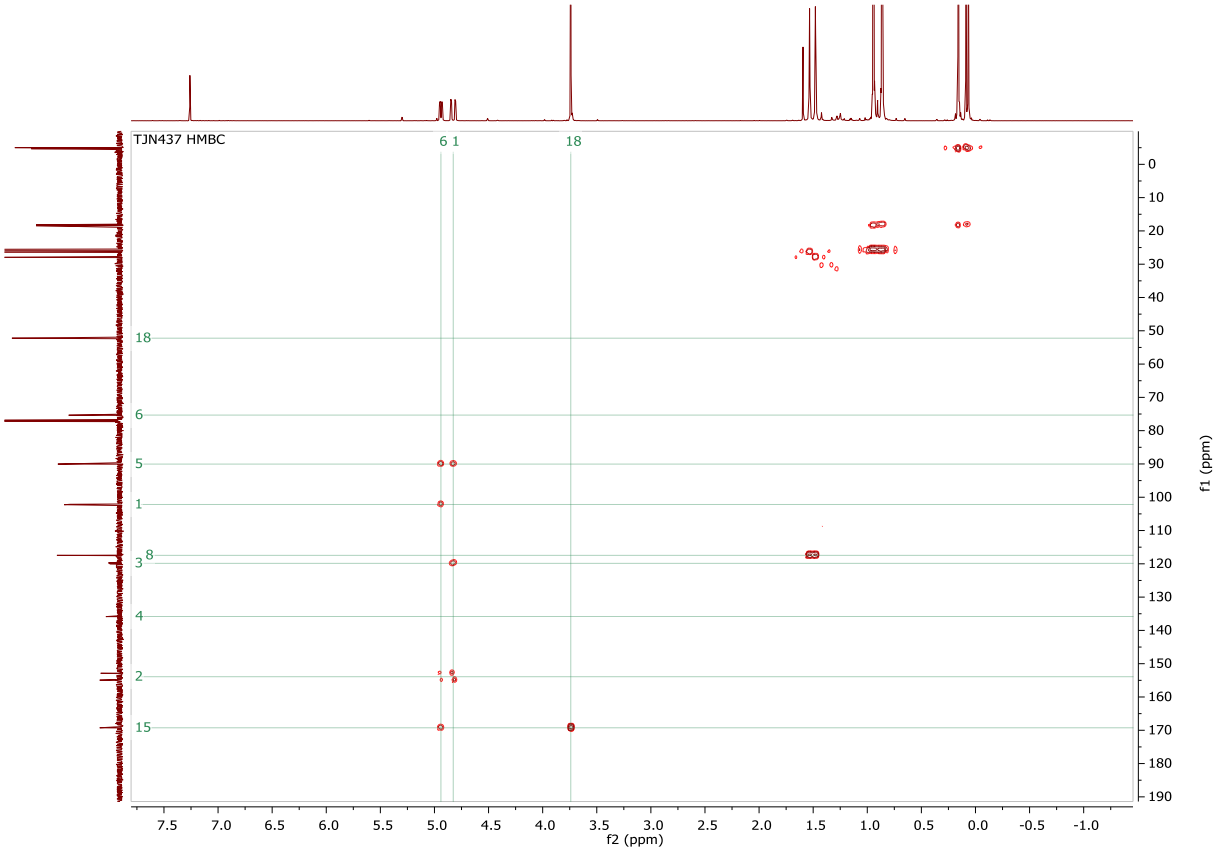





TJN437 PU [CDCl3] 19F
14 (dd)
-126.9
J(11.4, 5.8)
14
f1 (ppm)


TJN437 COSY
6 1
18
18
6 1
f2 (ppm)
f1 (ppm)

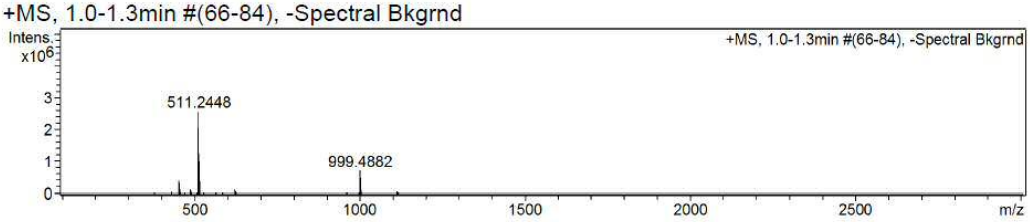

TJN437 HSQC
6 1
18
18
6
5
1
8
3
4
2
15
f2 (ppm)
f1 (ppm)


TJN437 HMBC
6 1
18
18
6
5
1
8
3
4
2
15
f2 (ppm)
f1 (ppm)

Confirmation of Expected Formula

Sample-ID	tn_sel_TJN437	Submitter	tjn30 Toby Nash
Analysis Name	tn_sel_TJN437_353757_25_01_59441.d	Supervisor	sl288 Simon Lewis
Method used	Confirm Formula Positive 50to1500 loop inj.m	Acquisition Date	12/10/2017 10:51:57
Ionisation Mode	positive electrospray (ESI)		

+MS, 1.0-1.3min #(66-84), -Spectral Bkgrnd



#	m/z	I	I %	Area	S/N
1	453.1959	397260	15.5	18362	4196.0
2	454.1936	153751	6.0	7185	1615.0
3	489.2516	138825	5.4	6728	1221.9
4	511.2448	2568296	100.0	81743	20518.9
5	512.2485	1261404	49.1	50797	10035.5
6	513.2394	502848	19.6	23308	3984.1
7	623.3250	143229	5.6	9407	1122.4
8	999.4882	708202	27.6	42353	6764.5
9	1000.4888	480621	18.7	33390	4602.7
10	1001.4840	274971	10.7	22410	2640.2